Exhibit 1

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW JERSEY

IN RE BIOGEN '755 PATENT LITIGATION	Case No. 10-cv-02734 (CCC) (JAD)

September 7, 2011
9:35 a.m.

VIDEOTAPED DEPOSITION of DAVID JACKSON, an Expert Witness on behalf of Biogen, taken by Defendants, held at the offices of Paul Weiss Rifkind Wharton & Garrison located at 1285 Avenue of the Americas, New York, New York, before Eileen Mulvenna, CSR/RMR, Certified Shorthand Reporter, Registered Merit Reporter and Notary Public of the State of New York.

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IT IS HEREBY STIPULATED AND AGREED, by and between the attorneys for the respective parties herein, that filing and sealing be and the same are hereby waived.

IT IS FURTHER STIPULATED AND AGREED that all objections, except as to the form of the question, shall be reserved to the time of the trial.

IT IS FURTHER STIPULATED AND AGREED that the within deposition may be signed and sworn to before any officer authorized to administer an oath, with the same force and effect as if signed and sworn to before the officer before whom the within deposition was taken.

DAVID JACKSON

THE VIDEOGRAPHER: Good morning.

My name is -- please note that all the microphones are sensitive and may pick up whispering and private conversations. Please turn off cell phones or place them away from the microphones as they can interfere with deposition audio. Recording will continue until all parties agree to go off the record.

My name is Pete Cooper representing Veritext New York.

The date today is September 7, 2011, and the time is approximately 9:35 a.m.

This deposition is being held at Paul Weiss Rifkind Wharton & Garrison located at 1285 Avenue of the Americas in New York, New York and is being taken by the counsel for the defendant.

The caption of this case is In Re: Biogen '755 Patent Litigation. This case is filed in the United States District Court for the District of New Jersey, Civil Action No. 10-cv-02734.

The name of the witness is

DAVID JACKSON

David Jackson.

At this time the attorneys present in the room and attending remotely will identify themselves and the parties they represent.

MR. GROOMBRIDGE: Nicholas Groombridge on behalf of Biogen.

MR. SANDEL: Peter Sandel on behalf of Biogen.

MS. HURLEY: Elizabeth Hurley, Biogen Idec.

MS. NYARADY: Catherine Nyarady on behalf of Biogen.

MR. BARSKY: Wayne Barsky, Gibson Dunn, on behalf of Merck Serono and Pfizer.

MR. BEST: Tim Best, also Gibson Dunn, also on behalf of EMD Serono and Pfizer.

MR. BERL: David Berl, Williams & Connolly, on behalf of Bayer.

MR. GENDERSON: Bruce Genderson, also with Williams & Connolly, on behalf of Bayer.

MS. SIMPSON: Jamie Simpson, also

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with Williams & Connolly, on behalf Bayer.

MR. PARKER: Greg Parker from White & Case on behalf of Novartis.

THE VIDEOGRAPHER: Thank you.

Our court reporter, Eileen Mulvenna, representing Veritext will swear in the witness and we can proceed.

DAVID JACKSON,

having been duly sworn by Eileen Mulvenna, a Notary Public of the State of New York, was examined and testified as follows:

EXAMINATION

BY MR. BARSKY:

Q. Good morning, Dr. Jackson.

A. Good morning.

Q. In front of you I've placed three exhibits.

Exhibit 1 is your initial declaration in connection with the claim construction proceedings in this case.

Exhibit 2 is your responsive declaration.

And Exhibit 3 is a copy of what we'll refer to as the '755 patent.

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A. Okay.

Q. Is that how you also refer to that patent?

A. Yes.

(Jackson Exhibit 1, No Bates numbers, Expert Declaration of David A. Jackson, Ph.D., marked for identification.)

(Jackson Exhibit 2, No Bates numbers, Responsive Expert Declaration of David A. Jackson, Ph.D., marked for identification.)

(Jackson Exhibit 3, Bates Nos. BIMA0000001 through 45, US Patent No. 7,588,755, marked for identification.)

MR. BARSKY: Does anyone need extra copies of any of those documents? Because I have a few left still. Okay.

BY MR. BARSKY:

Q. We're going to be using some specific terms. And I thought we would spend just a few moments clarifying our respective meanings of those terms.

In the course of your reports, and in the '755 patent itself, there are references

to polypeptide.

You're aware of that?

A. Correct.

Q. And there are also references to protein; correct?

A. Yes.

Q. In the '755 patent, there is a specific definition of polypeptide.

Did you see that?

A. I did.

Q. And for purposes of your initial and responsive expert reports and for purposes of your analysis and opinions in this case, have you used the definition of polypeptide set forth in the '755 patent?

A. Well, as I explained in my responsive declaration, the way the term "polypeptide" and the frequently interchangeably used term "protein" are actually used in the scientific literature is, as I indicated there, largely interchangeable.

I did, however, make the distinction in saying that there was -- to the extent that there was a difference between the two, there was

a tendency for "polypeptide" or "polypeptide chain" to be used to -- when talking about a -- I need another third word now here -- talking about a string of amino acid residues hooked together by peptide bonds to be used for what you might call just a primary sequence of the protein, that is to say the sequential string of amino acid residues without some of the covalent modifications that often occur, particularly in a cellular context.

And similarly, there is a tendency, although even less pronounced, I think, for the word "protein" to be used when referring to a fully modified mature protein or polypeptide chain, which may have a whole variety different kinds of posttranslational modifications or other kind of covalent modifications to it.

But the key point, and the reason I put this in my responsive declaration, was really to assist the court in not getting sidetracked by trying to parse distinctions between "polypeptide" or "polypeptide chain" and "protein" because they really are, in scientific discourse in 1980 and now and also in the

scientific literature, used largely interchangeably.

Q. So for purposes of your analysis and opinions in this case, did you use and rely on a specific definition of polypeptide that appears in the '755 patent, or did you rely on what you understood a person of skill working in 1980 would have understood about those terms? In other words that they were used loosely and interchangeably?

A. More the latter than the former. The definition that is given in the patent is fine as far as it goes. It just doesn't go far enough and it doesn't -- it's not limiting in the sense. That's because, as I say, "protein" and "polypeptide" can be used interchangeably. That was the primary point I was trying to make.

Q. In the --

A. And that's the way I understood it, just to respond directly to your question.

Q. And that's the way you understood what?

A. That's the way I thought about the term "polypeptide" as something that was

interchangeable with "protein."

Q. So for purposes of your opinions, you did not apply the specific definition of polypeptide that appears at Column 8, lines 61 to 64 or so; is that correct?

A. May I refresh my memory as to just what that is?

Q. Sure, yeah. It's Column 8, and I believe it starts at line 61, 62.

A. 62.

(Witness peruses the exhibit.)

A. I certainly used that --

Q. Excuse me, Dr. Jackson --

A. Should I read it out?

Q. -- why don't you read it into the record so we're on the same page and then you can answer the question.

A. So the definition of polypeptide in the '755 patent at Column 8, line 62, is "Polypeptide - a linear array of amino acids connected one to the other by peptide bonds between the alpha amino acid and carboxy groups of adjacent amino acids."

Q. Now, would you go ahead and answer

the question as to whether or not, for purposes of your analysis and opinions, you used that specific deposition of polypeptide that appears in the '755 patent?

A. Okay. And as I said, yes, to the -- as far as this goes, I did; but I didn't use it as a limiting definition. In other words, this definition is asking one to make assumptions one way or the other because it's silent on the topic of whether the amino acid residues referred to here are modified or not.

Q. It is silent as to that point.

Are there portions of your initial or responsive expert declarations in this case where the opinions that you expressed or the observations that you made are dependent more on what you have described as this loose or interchangeable uses of the words "polypeptide" and "protein" as opposed to the specific definition that appears in Column 8? And feel free to make reference to Exhibits 1 and 2 if you need to.

A. Okay. Because I -- if you have some places in here where I specifically used that

that you'd like to point me to, I'd be glad to speed up the process. I genuinely don't know the answer to that question without looking at --

Q. That's okay --

A. -- this --

Q. What we want to understand, Dr. Jackson, as you're flipping through this is whether there are portions of your report and your opinions that depend more on what you've described as this loose or interchangeable use of the term "polypeptide" as opposed to the more specific deposition that appears in the patent. That's the question.

And I don't have any specific portion of your reports in mind, but if, looking through it quickly now, anything pops out to you or if, during the day, you see something that strikes you as applicable more to one definition than the other, I would ask you to point that out.

A. Okay. Fair enough.

MR. GROOMBRIDGE: Will you give me a continuing objection to form to the extent that you're characterizing Dr. Jackson's

testimony in your questions?

MR. BARSKY: Fine.

MR. GROOMBRIDGE: Thank you.

BY MR. BARSKY:

Q. Do you want to take just a quick look now and see if anything pops out at you, without necessarily reading it word for word?

A. Right.

(Witness peruses the exhibit.)

A. Well, let's -- nothing occurs to me at this point. My tendency certainly would have been to use the broader more interchangeable definition between protein and polypeptide because that's the way I and other people in the field have always used the term. And I certainly didn't, as I was writing this, have the literal specific definition in a limiting sense that is found in the '755 patent in mind.

Q. Okay. Let me ask you to turn to your responsive report, which is Exhibit 2.

A. Uh-huh.

Q. And in particular, paragraph 3, which begins on page 2.

A. Okay.

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Q. You see there's a section there entitled -- Subsection A entitled "Protein and Polypeptide"?

A. On page 2, yes.

Q. Okay. And do you see that, around the middle of page 2, you offer a commentary on the distinction between a polypeptide and a protein?

A. Exactly.

Q. If I use the term "polypeptide" during the course of our discussion today, I'm going to be using it in the manner that it is referred to in the patent in Column 8, the manner in which it's defined, as well as in the manner that you recite here when you say that polypeptide, "tends to be used to refer to a sequence of amino acids linked by peptide bonds whether produced by translation of mRNA in a living cell or by chemical synthesis in a test tube."

A. So just for avoidance of confusion and clarification, does your use of that term explicitly imply that there are no chemical modifications, no covalent modifications

whatsoever of any of the amino acid chains -- any of the amino acid residues in that polypeptide?

Q. I believe if I were to have read the entire sentence into the record, it would have gone on to say, "without any chemical modifications to the amino acids and with no implication about its three-dimensional confirmation."

A. Sorry. That's what I said, but you were referring to the definition in '755, which doesn't say that.

Q. I see.

A. So that's what I'm trying --

Q. I'm just trying to come to an agreed --

A. If you will buy into that extended sentence there as how you're using it --

Q. Then what?

A. Then I will know how you're using it.

Q. Okay. Well, what you said in your report you considered to be an accurate definition of polypeptide; correct? In other words what I just read into the record.

A. Yeah, I think that's an accurate definition of polypeptide.

Q. And where do you -- where, if at all, do you see any distinction between what you've put in paragraph 3 of your responsive declaration and what appears as the explicit definition of polypeptide in the '755 patent?

A. Well, I've just expanded a little bit. This whole section and the subsequent section were written by me to try to assist the court in understanding terms that are used somewhat loosely and perhaps ambiguously in the scientific literature.

Q. But you understand for purposes of today's deposition, Dr. Jackson, we would like to have a more specific --

A. I -- I do.

Q. -- in mind.

So if I use the word "polypeptide" during the course of my questioning, unless I indicate otherwise, I am using it in the manner that you have defined in paragraph 3 of your --

A. Okay.

Q. -- responsive expert declaration and

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as it appears in Column 8 of the '755 patent --

A. Okay.

Q. -- and its explicit definition.

Will you understand that?

A. Yes.

Q. Okay.

MR. GROOMBRIDGE: Objection to the form there. I think that's a mischaracterization.

MR. BARSKY: Well, let's be clear.

MR. GROOMBRIDGE: Indeed, let's be clear.

MR. BARSKY: Any mischaracterization as to the way I'm using the term?

MR. GROOMBRIDGE: What you just said is contrary to the testimony that we've already had today inasmuch as you're taking something from the patent and something from Dr. Jackson's report and saying they're identical. You've already established testimony that that's not necessarily the case. So let's be clear. Why don't you spell out one single definition of what it is you plan to --

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MR. BARSKY: That's fine.

MR. GROOMBRIDGE: -- refer to as polypeptide.

MR. BARSKY: That's fine.

MR. GROOMBRIDGE: Not two of them with your editorial comments that the two are the same.

MR. BARSKY: That's fine. By the way, I disagree with what you just said, but never mind that.

BY MR. BARSKY:

Q. Dr. Jackson, if I use the word "polypeptide," I'll be using it as it is explicitly defined in Column 8 of the '755 patent.

A. Right.

Q. Will you understand that, sir?

A. Yes.

Q. Okay.

A. Thank you.

With that in mind.

Q. Why don't we turn to page -- excuse me -- to paragraph 18 of your responsive declaration.

mammalian system capable of glycosylating the interferon beta protein.

Do you have that in mind?

A. Yes.

Q. Do you agree that that protein is not necessarily different in structure than the native protein?

A. Since I'm not an expert on protein glycosylation in cells, I really don't know whether there are other mammalian cells that have been shown to put precisely the same glycosylation on -- at the same sites as occurs in human cells. I just don't know that, so I can't really answer that question.

Q. Is that the reason why you were careful not to rule that out in your report in paragraph --

A. To be perfectly honest, I didn't realize I was being careful about this point. I was not trying to make this particular point.

Q. Okay. Let's go back to the word "polypeptide" for a minute because I'm going to use it now in connection with this discussion that we just had.

A. Okay.

Q. With respect to the interferon beta polypeptide produced in a recombinant system, that polypeptide would be identical to the native polypeptide regardless of whether there are differences in posttranslational modifications, carbohydrate compositions and so on; correct?

A. Well, no. Let's make sure we're clear on this as well.

Q. Okay.

A. So interferon beta is, in human cells, produced as a peptide chain which is longer than the mature native interferon beta. And so there's an internal sequence that is cleaved off that. So to that extent --

Q. Yes, go ahead.

A. To that extent, the structures might well be different.

Q. I'll rephrase the question.

A. Okay.

Q. Would you agree that the polypeptide of a mature recombinant beta interferon protein would be identical to the polypeptide of native interferon beta in its mature form regardless of

whether the proteins may be the same or different?

A. So you're asking if the primary product of translation in a cell containing a recombinant DNA molecule would produce a polypeptide, using the definition in the '755 patent of polypeptide, that is -- or could be identical to the polypeptide that is produced in human cells as the native protein? Is that what you're asking?

Q. It's very close. We're trying to compare two things.

A. Okay.

Q. And I'm going to ask you to compare two things.

On the one hand a recombinant interferon beta polypeptide in its mature form.

A. Right.

Q. On the other hand, a native interferon beta also in its mature form.

A. Uh-huh.

Q. And I'm asking you now whether the polypeptides of those two proteins are identical regardless of whether the proteins themselves are

identical.

A. It would depend on what the construct was that you used to make the recombinant polypeptide, but I think it ought to be possible, and I think it has been possible, to make a recombinant polypeptide that would be the same in structure -- in its primary structure as the one that's found in human cells.

Q. You say you think it has been possible. What do you mean by that?

A. I suspect that in all of the work that was done on beta interferon, somebody has -- somebody did that. I think I remember that that work has been done, but I'm not -- I couldn't give you a citation to it and I don't know that for sure.

Q. By "that work" having been done, you mean that a recombinant beta interferon was produced in a form in which the polypeptide was identical to the native beta interferon; correct?

A. In terms of its amino acid sequence, yes.

Q. In terms of the polypeptide as defined in the '755 patent --

A. Well --

Q. -- correct?

A. -- that's the amino acid sequence; right? So the complete amino acid sequence, the primary structure and the polypeptide are all interchangeable terms, I believe, in terms of the definition given there in '755.

Q. Okay. Do you remember what work was done --

A. I don't. I'm sorry.

Q. Okay. Do you recall an article by a gentleman named Kagawa?

A. I know the name; but I don't recall the specific article, no.

Q. That would be true, by the way, that you could have identical polypeptides in both native and recombinant beta interferon, regardless of the host system in which the protein was produced, provided that in both cases you are looking at the mature form of the protein; correct?

A. I think that's correct.

Q. Bear with me one second --

A. Sure.

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Q. -- while I get organized here.

(Pause from the record.)

MR. BARSKY: Can we mark this, please.

(Jackson Exhibit 5, Bates Nos. S00020660 through 670, Response from Patent Office, marked for identification.)

BY MR. BARSKY:

Q. Dr. Jackson, the reporter has placed before you a copy of Exhibit 5, which I will represent to you is a response to an office action in the '503 application, which is related to the '755 patent. And I'm going to refer you to just some specific comments in here in a moment, but I just wanted to ask you to just take a moment and breeze through it and tell me if you think you've seen it before.

MR. GROOMBRIDGE: Is there an Exhibit 4?

MR. BARSKY: There is.

MR. GROOMBRIDGE: But we haven't gotten to it yet?

MR. BARSKY: No.

(Witness peruses the exhibit.)

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BY MR. BARSKY:

Q. Any of that look familiar to you?

A. Well, some of the topics certainly look familiar, but as you know, there were a lot of exchanges with the Patent Office that discussed similar kinds of topics.

Q. I'm actually just asking if you the document itself is familiar to you, not if the material in it is familiar to you.

A. In fact, I don't believe I have seen this specific document before.

Q. Okay. Let me ask you to kindly turn to page 9 of Exhibit 5.

A. Okay.

Q. And you should feel free to read as much of the context as you would like, but I will represent to you that the discussion here is with respect to the understanding in the art as of 1980 --

A. Okay.

Q. -- or thereabouts.

A. Okay.

Q. All right. On page 9, there's a paragraph that appears right in the middle of the

page that begins with the words "Wholly apart."
Do you see that?
A. Yes.
Q. Would you just take a moment and read that paragraph to yourself?
A. Uh-huh.
Q. Thank you.
(Witness peruses the exhibit.)
A. You'd like me to go on and read the listing A through G of the particular difficulties --
Q. If you'd like to, go right ahead.
A. I thought that might be part of the context.
Q. We will get to that, but if you'd like to read that as part of the context, you're free to do that.
A. Okay.
(Witness peruses the exhibit.)
A. Okay.
Q. Let me just ask you in general whether you agree with the two paragraphs that you read as a -- to the extent they refer to the state of the art in 1980.

A. I agree -- so what these paragraphs do is to make the point that it was anticipated to be difficult to produce any particular recombinant DNA -- any particular protein, human protein, from a recombinant gene at this time.

And then it listed a number of possible reasons as to why mechanistically and -- series of mechanistic steps as to where there might be difficulties. And so if you're asking do I agree with the overall notion that this was a difficult thing to do in 1980, yes, I do.

Q. Okay. What about the statement at the -- and I'll read it into the record so you know exactly which statement I'm referring to.

A. Okay.

Q. "In fact, researchers in the art of molecular biology were seriously concerned that attempts to produce any particular mammalian protein in bacteria would be fraught with problems."

Do you agree with that as a statement to the extent that it refers to the art in 1980?

A. Basically, I do. There were still a

lot of problems at that -- at that time. Some of them had started to become solved, but as somebody who's responsible for groups doing this kind of work at the time, there were lots of problems still there, yes.

Q. For purposes of your opinion and your analysis, you defined what you considered to have been a person of skill in the art as of 1980; correct?

A. I did.

Q. And you were working in this art --

A. I was.

Q. -- in 1980?

And do you consider that you were a person of at least ordinary skill in the art as of 1980?

A. Yes.

Q. And do you agree that a person of skill in the art working in 1980 would be seriously concerned about his or her ability to express mammalian protein in bacteria?

A. In general, yes, but let me make one -- one qualification I think may be helpful going forward.

It's one thing to be able to express a mammalian protein from a recombinant gene at a level of one or two molecules per cell. So, you know, you can write a scientific paper on that. You can say I've demonstrated expression. To the extent that it is a weigh station to where one is trying to get, it's a very useful thing to have done. If you can get a little bit of expression, then it's -- that points you in a direction in which you can maybe get much more.

But the goal was, in virtually all cases, to make large amounts, commercially useful amounts, medical application useful amounts, of these proteins in the cells.

And so if that's what we mean by "expression," then yes, I think most people at that time who were skilled in the art had real concerns about being able to produce many mammalian cells in -- from recombinant genes. Many mammalian proteins from recombinant --

Q. Thank you. In bacteria?

A. In bacteria, yes.

Q. When in your view was -- were these problems solved such that a person working in

this field could reasonably expected to produce a mammalian protein in E. coli, let's say?

A. Well, that technology has really evolved over the course of the last 30 years. For any particular protein, it still is not necessarily trivial to produce commercially substantial quantities, commercially relevant quantities of a protein from recombinant constructs even today.

The technology is so good today that the probability of being able to do that ultimately -- if you're willing to invest the resources to try a whole bunch of different things, the probability is pretty good and much higher than it was back in 1980.

But I would assert that there is no general formula that you can apply that will allow you to produce an unknown protein in bacterial cells easily even today.

Q. Okay. Are you speaking of -- only of nonbacterial genes?

A. Actually, not -- not -- well, probably -- yeah, probably nonbacterial genes. Bacterial -- although certain very distantly

related bacterial genes, you can occasionally have problems in expressing them; but in general, prokaryotic genes are expressed more readily in prokaryots than eukaryotic genes are, whether those genes are from higher or lower eukaryots.

Q. At what point in time, either a year or range of years, do you believe that the field ceased to be fraught with problems, as suggested in Exhibit 5?

A. Well, that depends on what -- what your definition of "fraught" is. Could you maybe expand on that a little bit?

Q. Well, how about the problems that are itemized beginning on page 9 continuing on page 10 in subparagraphs A through G? I believe that is probably among the references by the author here.

So at what point that time do you think a person of skill working in this field would have ceased to view the expression of a nonbacterial gene in a bacterial host system as being fraught with problems?

A. Okay. So let me try this answer and see if it gets to what you want.

I think that by probably the early '90s, the technology had improved enough so that there was a reasonable expectation that, if you tried hard enough -- and sometimes that might be trying very hard indeed -- if you tried hard enough, you could express almost any protein from a eukaryotic source in bacteria.

Q. When you just used the verb "express" in your answer, were you referring to expression in what you described earlier as nontrivial or potentially commercial --

A. Yes --

Q. -- quantities?

A. -- I was.

Q. What if we were to change the definition of expression that we're using; would your answer change? For example, if I were to suggest that expression is -- let me start over again.

What if we were to agree that expression for purposes of this discussion means the ability of a transformed cell to express any quantity of a recombinant polypeptide --

A. Right.

Q. -- or protein regardless of whether that cell or culture could be harnessed to be produced in commercially significant quantities; would your answer change with respect to whether a person of skill would have viewed the expression of a nonbacterial gene in a bacterial system as being fraught with problems?

A. And you want to know when such a person of ordinary skill in the art --

Q. Thank you, yes.

A. Okay. It's obviously in the general case, although not always in every specific case, easier to express very small quantities than it is to express the large quantities. And so it would have been sooner, maybe say the mid to late 1980s as opposed to the early to mid 1990s, for the large quantities that I'm talking about. That's the distinction you're looking for?

Q. Thank you, yes. You've answered my question.

So up until that time, the mid to late 1980s, a person of skill working in this field would have viewed the expression of a nonbacterial gene in a bacterial host system as

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being fraught with problems --

MR. GROOMBRIDGE: Objection.

Q. -- right?

A. Well, I don't know exactly what "fraught" means, so -- I think such a person would have viewed the expression of a nonbacterial gene in bacterial systems as potentially having significant problems that would take significant time and resources to solve well into the 1980s.

Q. Now, the exhibit goes on to state, and I'll quote, "Successful expression of one mammalian protein in bacteria, such as somatostatin, could not and would not provide a basis for one of ordinary skill in the art to predict with a reasonable expectation of success that any specific mammalian protein, such as interferon beta, would be producible in transformed host cells."

Do you see that?

A. I do.

Q. Do you agree with that statement as a -- as to the state of the art in 1980?

A. I would agree with it without

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(Jackson Exhibit 9, Bates Nos. BIMA0010403 through 419, Amendment and Response, marked for identification.)

BY MR. BARSKY:

Q. Now, I've handed you an amendment and response filed in the '658 application.

Do you see that, sir?

A. Yes. There's the number, okay.

Q. And it's dated July 16, 1996?

A. Yes.

Q. And this particular filing includes Claim 31 as it stood when the claims were rejected in the earlier office action that you looked at.

Do you see that?

A. That would be at the bottom of the page below the line that's drawn across?

Q. Exactly, where it says --

A. Where it says "31 amended."

Q. Exactly.

A. Okay.

Q. Do you see that in the preamble of Claim 31 in this Exhibit 9, that there's a reference to "administering a therapeutically

effective amount of a composition"?

MR. GROOMBRIDGE: Objection.

A. I see those words there. I'm not sure whether that's in the preamble or not. I'm not clear precisely what the breakdown between the preamble and the body in these claims is.

Q. Okay. But you see that there's a references to the administering -- excuse me.

You see there's a reference to "administering a therapeutically effective amount of a composition"?

A. Yes.

Q. Okay. And you also see that, in Claim 31, it has the same language as appears in Claim 1 of the '755 patent, beginning with the words, "A polypeptide produced by a nonhuman host transformed by a recombinant DNA molecule"?

Do you see that?

A. Yes.

Q. And do you understand that the words in brackets are words that have been deleted --

A. Deleted, yes.

Q. -- right?

Going back to Exhibit 8, when the

applicant told the Patent Office that Claim 31 of the '658 application also -- quote -- "also recites those positive process steps," do you have an opinion as to what that referred to in Claim 31 of the '658 application now that you've looked at it?

A. Well, as I've said in my responsive declaration, the process step in this claim, it seems to me, is the step of administering a therapeutically effective amount of the composition comprising, and then there's a long description that comes below as to what that composition consists of.

Q. And in your answer you said "this claim."

What were you referring to? Were you referring to Claim 31 of the '658 application?

A. I thought I was.

Q. Okay. I just wanted to clarify.

And so the words that were used to communicate with the Patent Office by the applicant are "positive process steps," plural; correct?

A. That's right.

Q. And so my question to you was, do you have an opinion as to what the applicant was referring to when the applicant told the Patent Office that Claim 31 of the '658 application also recited "those positive process steps"?

A. Yeah, my opinion is that what was being referred to is the step of administering a therapeutically effective amount of a composition. And that has got many complexities to it, and so that might have been what occasioned the use of the word "those" and "steps" in this case.

Q. Okay. Which complexities are you referring to now?

A. Well, if you're going to administer a therapeutically effective amount of a composition, there are various elements of administering, how much, under what regimen and in what -- with what other adjuvants or anything like that that you might use. That's an example of one type of complexity.

Q. So it's your testimony then that when the applicant said, "those positive process

steps" in referring to Claim 31 of the '658 application, the applicant was referring to the positive process step of administering; is that correct?

A. That's my interpretation, yes.

Q. How confident are you in that interpretation?

A. Well, if I look at the whole prosecution history, I'm pretty confident of that interpretation because it seems to me that as I've explained in my responsive declaration, that there are a number of cases where it is less ambiguous, in fact, it's quite unambiguous, and I agree that it is somewhat ambiguous here, that what's being referred to as the -- the positive process step is the step of administering a therapeutically effective amount of a composition and that, in many exchanges that I've seen in this file history, the use of the plural "positive process steps" is because they're referring to the same step in multiple patents, patent applications.

And, therefore --

Q. And --

A. -- when you understand it that way, the use of the plural is perfectly appropriate. And I think there is other internal evidence that that is what the examiner meant that I have cited in my responsive declaration and that I know Biogen attorneys have cited as well.

Q. The applicant is not referring in this particular response to anything other than Claim 31 of the '658 application; correct?

A. Uh-huh.

Q. Correct?

A. I believe that's true.

Q. And you're reading this as being the same as if the applicant had instead said that the Claim 31 of his copending '658 application also recites the same positive process step --

A. Uh-huh.

Q. -- is that correct?

A. I believe so.

Q. And would you agree that that is anomalous to read this as meaning the same thing, whether it says "those positive process step" or "the same positive process step"?

A. Yeah, I've already said that I

believe this is ambiguous. There are, I think, several instances of potential ambiguity in the extensive exchanges using much this same language that occurred between applicant and examiner. And it would have been clearer if -- and more precise, obviously, if they'd used the singular there, but they didn't. And I gave you a speculation as to why they might not have.

Q. You understand that the defendants are reading this particular reference to "positive process steps," as well as the other references to "positive process steps," in a manner that diverges from your --

A. I certainly do understand that.

Q. Would you agree that the section of Exhibit 8 that we've been focusing on in connection with the '658 application is consistent with the interpretation that the defendants are advancing for what those positive process steps are?

A. Yes, I would agree that it's consistent with that interpretation, which I believe to be erroneous.

Q. Okay. But you believe -- but you

will allow that it is consistent?

A. Yes.

Q. Okay.

A. Yes.

Q. All right. Let me ask you to turn back to Exhibit 4, please, the affidavit of Dr. Fiers. In particular, could you turn to page 40, please.

A. Okay.

Q. In the middle of that page, there's a Roman numeral with a heading.

Do you see that?

A. Yes, Roman numeral V.

Q. Can you just read that first sentence into the record, please.

A. Following 68? Or do you want the heading read that --

Q. The heading, just the first sentence of the heading.

A. "The complete DNA sequence that characterizes human beta interferon was publicly available by mid April 1980."

Q. And as someone who was working in the field at the time, were you aware that that

was the case?

A. I doubt that I was because that was actually a couple of months before I joined Genex Corporation.

Q. Since you have continued to work in this field and developed an expertise in connection with the subject matter of your reports and the '755 patent and worked on this particular case, is this information consistent with your current understanding of when the DNA sequence was available?

A. I believe it is.

Q. Okay. Why is that?

A. Because I believe that in terms of public availability, I think Taniguchi made that sequence information available sometime in the spring of 1980. I can't tell you at this point exactly when.

Q. Okay. And what's your understanding as to how Dr. Taniguchi made that -- made the complete DNA sequence for human beta interferon publicly available by that time?

A. I'm not sure I can tell you precisely. I know he gave a seminar in which he

talked about it, but I'm not clear to exactly what extent or even whether he disclosed the entire sequence at that time or maybe a partial sequence. And I can't tell you off the top of my head when this was actually published in the scientific literature.

Q. Okay. But in either event, it's your present understanding that the sequence was publicly available by mid April of 1980; correct?

A. I believe that's correct.

Q. Okay. Do you know Dr. Charles Weissmann?

A. I've met him on a couple of occasions at meetings, yes.

Q. Did you work with him at all in connection with your work on alpha interferon?

A. No.

Q. Let me ask you to turn to page 45, please. In particular, I'm going to ask you to focus on the sentence that -- the first complete sentence on this page --

A. Starting with "Dr. Taniguchi"?

Q. Exactly.

A. Yes.

DAVID JACKSON

Q. This says, "Dr. Taniguchi had, in fact, published his beta interferon DNA and amino acid sequences even earlier, May 1980."

And then there's citation to an article.

Do you see that?

A. Right.

Q. Is that consistent with your recollection and understanding?

A. As I've indicated, I am -- I don't have a specific recollection of dates. I remember that this became available in the spring of 1980.

Q. Okay.

A. So that would be consistent with this.

Q. Okay. Let me ask you to turn to page 32, please, in particular paragraph 55.

A. Okay.

Q. I'm going to direct your attention to just the last two sentences that appear in this paragraph; but if you'd like to read as much before or after, feel free, for context.

A. Is this paragraph 55?

A. Well, I have -- I have knowledge and expertise relative to a number of the issues that are discussed in the patent. I know more about some of them and less about others of them.

Q. And you have knowledge and expertise, for example, regarding cloning of genes; correct?

A. Yes.

Q. And expression of polypeptides; correct?

A. Yes.

Q. Including recombinant expression of polypeptides?

A. Yes.

Q. You spent a significant amount of your career on issues relating to expression of recombinant polypeptides?

A. I wouldn't say I've spent as much on expression as I've spent on the -- developing the cloning technology. I started that work when I was a postdoc at Paul Bert's laboratory at Stanford. And I'm actually the first author on the first publication that was published on recombinant DNA technology.

And so through much of the time that I was an academic in the 1970s, I continued to work on developing that technology and applying it to the tumor virus SV40.

Q. Were there any problems or issues that were discussed in the '755 patent that you thought you had insufficient expertise to render an opinion about?

A. As I said, I thought, that with the work that I did to help prepare myself on this, I could do an adequate job of assisting Biogen. If I hadn't felt that, I would have declined the assignment.

Q. I guess my question is, were there any parts of the '755 patent that discussed scientific issues that you thought to yourself that's not something I have enough knowledge about to participate?

A. I don't recall any at this point, no. I felt genuinely comfortable that I knew an adequate amount about the issues presented in the '755 patent and that, if I didn't, it was information that I could acquire.

Q. You understand that the

specification and the claims are interpreted through the lens of the hypothetical person of ordinary skill; right?

A. Yes.

Q. You thought that you, I think you said this morning, possessed sufficient education and expertise to meet those requirements as it related to the issues addressed in the '755 patent; right?

A. Yes.

Q. Now, have you ever treated a cancer patient?

A. No.

Q. Have you ever treated a patient with viral disease?

A. That's a little more complicated to answer. Since I'm not an MD, I have not treated any patient directly with my own hands.

When I was at DuPont Merck, one of my responsibilities, among others, was to head up the development program for the -- what became the anti-HIV drug Sustiva.

And one of the significant activities in that development program was

clinical trials of Sustiva. And I had MDs that worked for me, whose supervisor I was, who did treat patients. And I was quite heavily involved in design and monitoring the clinical trials and the clinical trial data.

So in that indirect sense, I've had responsibility in some sense. It's, though, not the kind of responsibility you have if you've got a medical license for treating patients.

Q. Have you ever treated any patients using interferon?

A. No.

Q. Have you ever treated a patient with MS?

A. No.

Q. Have you ever sought to down-regulate the immune system by administering a compound or protein?

A. Well, as I've said consistently, I'm not an MD, so I haven't -- anything that requires administering drugs to patients is not something that I have personally done.

Q. Do you have any expertise with respect to the dosing of interferon to treat

cancer?

A. It depends on what you mean by "expertise." That's something that in reading the literature, one learns about what kinds of doses others report are effective.

Q. But do you bring with you any particular insight in that regard? Anyone can read the literature. I can read the literature too, but I'm not an expert on dosing.

My question --

A. That's how you get insight, is by reading the literature and reading what knowledge other people have generated.

Q. Do you have any training in the area of, for example, treatment of multiple sclerosis?

A. No.

Q. Cancer?

A. Again, in the supervisory context, I have had some responsibility for MDs who were involved in clinical trials of compounds that we were developing.

Q. You said in your report you were very familiar with the field of molecular biology, including cloning and protein expression

in 1980; is that accurate?

A. Yes, I think that is accurate.

Q. Would you likewise say that you're very familiar with the field of clinical use of interferon in 1980?

A. No.

Q. Now, I don't want to retread some of the territory you covered this morning with respect to what the word "polypeptide" means in the '755 patent. I just wanted to make sure I understood your testimony and clarify a few things.

You've reviewed the '755 patent?

A. Yes.

Q. Does the '755 patent provide any description of a structural difference between native beta interferon and recombinant beta interferon produced by a mammalian host cell?

A. Certainly not. The '755 patent doesn't discuss at all recombinant interferon produced by a mammalian host cell.

Q. Let alone the structure of such a polypeptide; right?

A. Yes.

Q. And when we've been discussing in the last few questions mammalian host cell, it's obviously not limited to human -- I'm talking about human as well as nonhuman host mammalian cells; right?

A. Well, the '755 patent explicitly does not cover human host cells.

Q. So when you've been answering my questions about mammalian host cells, you've been thinking about nonhuman mammalian host cells?

A. Yes.

Q. Why don't you take a look at the definition of polypeptide in the '755 patent. I think it was at Column 8, line 62 to 64.

A. Right.

Q. Do you have that in front of you?

A. I do.

Q. And that definition provides no implication about the chemical or biochemical modification of any amino acid in the recombinant peptide; correct?

A. That's right.

Q. So any polypeptide that has that linear array sequence of the amino acid meets

that definition; is that right?

That was actually --

A. Meets that definition of what? Of being a polypeptide?

Q. That was inartfully asked. Let me -- why don't you go to the claim at the end of -- at the end of the patent.

A. Yes.

Q. Do you have Claim 1?

A. I do.

Q. And you understand that Claim 1 defines some set of DNA sequences that are contained in the recombinant DNA molecule; is that right?

A. Uh-huh.

Q. In Subpart A of the claim; is that right?

A. Uh-huh.

THE REPORTER: Yes?

Q. You have to say yes or no.

A. Yes.

Q. Those are DNA sequences which are capable of hybridizing to the probes that are listed there; right?

DAVID JACKSON

A. That's correct.

Q. And that set of DNA sequences corresponds to a set of amino acid sequences per the genetic code; right?

A. Yes.

Q. And so my question is, per the definition of polypeptide in Column 8, that any polypeptide that meets the amino acid sequence requirements of Claim 1 is within the scope of the recombinant polypeptide of the '755 patent without regard to any chemical or biochemical modification of any amino acid in the sequence?

MR. GROOMBRIDGE: Objection.

A. So again, let me understand -- let me make sure I understand what you're asking.

You're asking if a polypeptide whose primary sequence is one -- and by "primary sequence," I mean just the sequence of amino acids without modifications or whatever -- whose primary sequence is one that would be produced if a DNA sequence included in Subpart A here were used as the source of information, whether that polypeptide is within this claim?

Q. Yes.

A. I believe that's correct.

Q. Okay. And put another way, the -- you understand that -- I think you said in your report some proteins are phosphorylated and some are not; is that correct?

A. That's correct.

Q. You can have, for example, interferon in phosphorylated form or not phosphorylated form; correct?

A. That's right.

Q. Whether it's phosphorylated or not, it's the same polypeptide, the same linear array of amino acids; right?

A. It certainly is. Whether or not -- what its activity is may well depend upon whether that same sequence is phosphorylated or not, but the primary sequence of amino acids is the same.

Q. It's the same polypeptide applying the definition of --

A. It's the same polypeptide applying that definition.

Q. And you said something about its activity. The patent discloses that both phosphorylated and nonphosphorylated beta

interferon essentially have the same activity, doesn't it?

A. I don't recall that one way or the other.

Q. I'll refer you to Column 2 at about line 18.

(Witness peruses the exhibit.)

A. Sorry, Column 2, line 18?

Q. Right. You see the sentence that starts, "Although authentic" --

A. Right.

Q. -- "HU interferon" --

A. Right.

Q. -- "beta is glycosylated"?

Do you see that sentence?

A. Right.

Q. That paragraph of the patent discloses that unglycosylated interferons are equally as active as native glycosylated interferons; right?

A. I'm sorry, the problem is you said phosphorylated, and that's what I was trying to find.

Q. I'm sorry.

DAVID JACKSON

A. If you mean glycosylated, I agree with you.

Q. I asked you a few minutes ago whether the beta interferon is phosphorylated or not, it's the same polypeptide applying the Column 8 definition.

Do you recall that question?

A. Yes.

Q. Let me ask the same question with respect to glycosylation. Whether it's glycosylated or not, that beta interferon is the same polypeptide, applying the Column 8 definition; right?

A. Applying the Column 8 definition; right.

Q. So you're helping me, too.

You understand that Claim 1 covers both glycosylated and nonglycosylated recombinant polypeptide; right?

A. If it were glycosylated when it was produced in a nonhuman host, then it would, I think, be covered by Claim 1.

Q. Okay. In other words, if one administers a recombinant polypeptide that is not

glycosylated, one still can be practicing Claim 1?

A. I think one can be practicing Claim 1 whether you administer -- whether it's the glycosylated or nonglycosylated form.

Q. And both the glycosylated and nonglycosylated form of interferon beta was -- had been disclosed in the prior art, too; right?

A. I believe that's -- yes, that's correct.

Q. You mention in your expert report acetylation.

A. Yes.

Q. Is interferon beta acetylated?

A. Not to my knowledge.

Q. You mentioned phosphorylation in your report. Is beta interferon phosphorylated?

A. Again, not to my knowledge.

Q. And again, per the agreed-upon -- or strike that.

Per the definition in Column 8 of the patent, whether or not a recombinant interferon beta polypeptide is acetylated or not, it's the same recombinant polypeptide; right?

A. Yes.

Q. The same with phosphorylation?

A. Yes. Whether it would be active or not is another question.

Q. But as far as you know, there's no such thing as phosphorylation of interferon beta; right?

A. Right.

Q. I'm sorry if you've answered this before, but Claim 1 is not limited with respect to the nonhuman host that is used to produce the recombinant polypeptide; correct?

A. That's right.

Q. It covers production of the nonhuman host in bacterial and mammalian cells alike?

A. Nonhuman mammalian cells.

Q. And yeast cells and --

A. And yeast, right.

Q. Had the glycosylation site of beta interferon been elucidated by the middle of 1980?

A. I don't know the answer to that.

Q. Had the particular sugar that is added to beta interferon been determined by middle of 1980?

A. Again, I don't know definitively, but I would doubt that because that's -- that kind of carbohydrate technology was not particularly well developed at that point in time.

Q. If -- if one had recombinantly produced beta interferon from a nonhuman mammalian host cell in one hand --

Are you with me so far?

A. Yes.

Q. -- and native human beta interferon that had been isolated in the other hand, in 1980, would you have been able to tell the difference by virtue of the glycosylation of which was which?

A. It would depend on what the nonhuman mammalian host was.

Q. Can you explain that further?

A. Well, as I said this morning, different mammalian and other higher eukaryotic cell lines have different glycosylation patterns. And so certainly the composition and sequence and to some extent the exact position of the glycosylation can vary on the same protein if

it's produced in different hosts.

Q. So with respect to some mammalian hosts, it's your testimony that you could have determined that it was recombinantly produced rather than native human interferon; but with respect to other mammalian hosts, you could not have determined?

A. I'm sorry, if that is your question, I misunderstood the original question. The question I thought you were asking was whether you could tell the difference between the native human interferon and a recombinantly produced interferon in some nonhuman host.

And my answer to that question is it depends on what the nonhuman host is. If there's a nonhuman mammalian host that has exactly the same glycosylation pattern as human cells do, then, by definition, the two compounds would be the same and you couldn't distinguish them.

Q. But in 1980, you didn't know what the native glycosylation pattern was, did you?

A. That's right. I'm sorry, I thought you were asking a hypothetical question and I was answering a hypothetical question.

DAVID JACKSON

Q. Sorry. Let me be more clear then. I apologize.

In 1980, would one have been able to tell the difference and determine which was which as between human native beta interferon that had been isolated on the one hand and recombinantly produced in a nonhuman mammalian cell beta interferon on the other hand?

A. So either I'm misunderstanding the question or we're somehow not communicating because my answer has to be the same. Again it depends on what the nonhuman mammalian host is.

Q. Okay.

A. If it puts the same glycosylation pattern onto the beta interferon -- oh, so when you say "in 1980," so -- I'm sorry, I didn't consider this possibly.

No, you couldn't do it in 1980 because there weren't any mammalian hosts that could be used to produce recombinant DNA molecules. Is that what you were --

Q. Fair enough. That's an answer to the question, I guess.

Now, make one more assumption, which

is that I now am able to produce in a nonhuman mammalian host cell recombinant beta interferon. And that's now in your left hand.

A. Yes.

Q. You have a flask with what I've produced.

A. Yes.

Q. Even though you don't think that could have been done in 1980; right? You don't think I could have done that in 1980; right?

A. Depends how dilute it was.

Q. And in your right hand, you have native interferon that's been isolated. Based on what was known in June of 1980, could you have determined which of the two flasks had the recombinantly produced beta interferon and which of the two flasks had the native isolated beta interferon?

A. It depends on what the mammalian host was.

Q. Do which mammalian hosts could you not have determined that?

A. Ones that -- ones that put on the same glycosylation as human cells do.

DAVID JACKSON

Q. But -- what glycosylation is that?

A. I mean, I can't tell you what the structure of it is.

Q. No one -- that was known in 1980; right?

A. Oh, whether it was known with respect to the absolute sequence of the sugar residues, I don't know; but you could certainly get the glycosyl residues off the protein. There are glycosylates that will do that. And there were pretty sophisticated gas chromatographic and maybe even by that time mass spec analyses by which I think you probably could have determined pretty definitively whether the glycosylation was the same or not.

Q. Okay. And let's for a moment assume that one does that analysis in 1980 and finds two different glycosylation patterns. Okay?

A. Then --

Q. You with me?

How do you know which one was human and which one was recombinantly produced in a nonmammalian --

A. You label your flask.

Q. I'm telling you flasks are labeled A and B. I'm asking for you to determine it.

A. Yes. So you'd say how do you know which one is the native one, and it's the one that you pulled out of the flask. You're saying, okay, you know what it is, but it's a blindfold test for me.

Q. Yes.

A. Ah, that's a different question. So now I understand.

Q. Okay.

A. So what I would have done is go to authentic native glycosylated interferon isolated from human sources, defined what that was and then compared it with both of the two flasks that you handed me with their labels obscured. And I would say either one of them is the same and one of them is not or they're both the same.

In the case where one of them is the same, then I would say the other one is recombinant. In the case when they're both the same, I would say I don't know.

Q. And is there such a thing as a single glycosylation pattern for authentic native

beta interferon?

A. I don't know in detail whether that's true.

Q. That's heterogenous amongst, for example, the population; right? You won't have the same glycosylation pattern necessarily that I will in my beta interferon; correct?

A. I don't know the answer to that.

Q. Even within the same person, there can be different glycosylation patterns; correct?

A. There can be, but you're asking the question specifically with respect to beta interferon, and I don't know the answer to that. But the point that you by implication are making, that there is heterogeneity in glycosylation of proteins, is in many cases correct.

Q. And which means if that's the case, there's not a single standard against which to compare to determine whether the glycosylation pattern is the same as native beta interferon; right?

A. Well, no, I don't think that's -- you do this analysis on the glycosylation and you're going to get a result. Okay. That result

provides an operational definition of what the sugar residues on the particular preparation of protein that you started with were.

Okay. That may or may not be heterogenous. Let's assume it is heterogenous. There will nonetheless be a signature with respect to that heterogeneity. I don't know how broad that is. I don't know what would happen if you went out and you collected serum from ten other individuals and pooled it and similarly determined the glycosylation pattern.

And I don't know what the variation would be in a cell line that was nonhuman that glycosylated because there may well be heterogeneity within a given cell line. There are multiple glycosylations around.

So one of the reasons this wasn't very well characterized at the time, it's really complicated chemistry. So a lot of the questions that you're asking I think want a degree of sort of rigor and specificity in the standards that I don't think was available.

And so the best you could have done is to look at what signal you get from authentic

beta interferon and look at what signal you get doing the same kind of analysis from the other samples. And if they're the same, then you either have to conclude that it's authentic beta interferon or you have to conclude that it's a nonmammalian cell line that puts on that -- as best your analytical methods can determine, the same glycosylation pattern. That's the real world.

Q. Let's change the hypothetical slightly. I'll give you a single flask that has interferon beta in June of 1980.

And my question is, can you tell me in June of 1980 whether that beta interferon was produced recombinantly by a nonhuman mammalian host or whether it was beta-isolated beta interferon?

A. Again, presuming that in 1980 there were a nonhuman mammalian host that could produce it, which as far as we know there wasn't -- I mean, this is getting really pretty deep into hypotheticals. I think my only honest answer in that situation is I don't know.

Q. Nothing in the patent leads you to

an answer one way or the other; is that fair to say?

A. I think that's fair to say.

Q. You talked about biochemical and chemical modifications of amino acids in your report. Other than the glycosylation that we've been discussing, are you aware of any such modifications that occur with respect to interferon beta?

A. No.

MR. BERL: We've been going about an hour. I'm at a breaking point. Do you want to take a little break?

MR. GROOMBRIDGE: Sounds good.

THE VIDEOGRAPHER: The time is approximately 2:43 p.m. This is the end of Media No. 3. We are off the record.

(Recess from the record.)

THE VIDEOGRAPHER: The time is approximately 2:53 p.m. This is the beginning of Media No. 4. We are on the record.

BY MR. BERL:

Q. Before we move to another topic, are

there any textbooks in the area of molecular and cellular biology that you consider authoritative?

A. Yes.

Q. What would that or those be?

A. Well, Jim Watson's "The Molecular Biology of the Gene," which is now in its probably sixth or seventh or eighth edition, is one of the classics in the area.

Benjamin Lewin has a textbook on molecular and cell biology, which is very good.

A little bit off to the side, Lubert Stryer's book on biochemistry and molecular biology is an excellent textbook.

And those are three examples.

Q. You agree that in your expert report, you refer repeatedly to transformation as a process; is that correct?

A. Yes, in certain contexts, it absolutely is a process.

Q. And including in the context in which you used it in your expert report; correct?

A. Well, I don't know whether that's true in every instance because it can certainly be used as an adjective as well as, for instance,

Dr. Ravetch did in his expert report.

Q. But at least in some instances, you used it as a process?

A. Sure, yes.

Q. And likewise you used the term "expressed" or "produced" to refer to a process, too; is that right?

A. Yes.

Q. In fact, you noted in your first expert declaration that the specification of the Fiers patent provides a definition for expression as "the process undergone by a structural gene to produce a polypeptide, it is a combination of transcription translation"; is that right?

A. Yes.

Q. So you agree that the specification defines expression as a process; is that right?

A. Actually, I don't know whether there is an explicit definition of that as a process.

Q. You can refer to paragraph 32 of your first expert report. That's Exhibit 1, I believe. And it's on page 20, near the bottom.

(Witness peruses the exhibit.)

Q. You see the sentence that begins,

"The specification of the Fiers patent also provides a definition for expression as 'the process'," and then you continue?

A. "To produce a polypeptide, it is a combination of transcription translation," yes.

Q. And so you agree that the specification defines expression as a process; is that right?

A. Yes.

Q. And production is also a process; is that right?

A. Yes.

Q. And there are two steps, you say in that same paragraph, two primary steps to a protein or polypeptide synthesis in the cell; is that right? And it's the same paragraph, the middle of the page.

A. I put that away prematurely. That was page 20, I think you said?

Q. Right. Paragraph 32.

(Witness peruses the exhibit.)

A. Here we go. I'm sorry, could you --

Q. It says -- do you see the sentence that says, "As I explained earlier, there are two

primary steps to protein or polypeptide synthesis in a cell"?

A. Yes.

Q. And those two steps are transcription and translation; is that right?

A. Yes.

Q. What do you mean by "two primary steps"?

A. Well, so the first step -- the first primary step, as I've said here, is transcription, but there are this series of discrete molecular events that have to occur in order for transcription to initiate and start proceeding. And then there's another series of discrete molecular events that have to occur for translation -- transcription to terminate at the appropriate point.

So I think that's probably why I said there are two primary -- maybe I should have said principal or overarching -- steps.

Q. Then the series of what you've called molecular events together constitute a step?

A. Yes.

Q. And is it likewise correct to say that there are two principal or primary steps to recombinant polypeptide production, the first being the introduction into a host cell line of recombinant DNA and the second being that the host cell expresses the recombinant polypeptide?

A. I think that would be one way of characterizing it. You could break it down in other ways as well, but those are two of a number of component actions that have to occur or steps that have to occur in order for you ultimately to -- for the cell to produce a recombinant polypeptide.

Q. You're aware that the parties in this case dispute the meaning of the language or the effect of the language "produced by a nonhuman host transformed by recombinant DNA molecule"; right?

A. My -- I think I would characterize it in a somewhat different way. I think in effect what is being argued here is a grammatical point, whether these, in fact, constitute two distinct steps that are defined as processes or whether, in fact, these are just part of an

adjectival phrase that modifies "recombinant polypeptide," which is itself part of the process step as the people from Biogen see it.

Q. And you would agree that that language limits the process by which a recombinant DNA -- by which a recombinant polypeptide is prepared, don't you?

A. Well, it limits it in the sense that if you're going to make a recombinant polypeptide, there's got to be DNA involved which is put into some kind of vector which is put into a host cell. And that host cell has got to be able to synthesize protein from that DNA, so the construct has to be one that enables that to occur in the particular host cell, sure.

Q. And in principle, one could prepare a recombinant polypeptide using a human host cell; correct?

A. Sure.

Q. And preparation of a recombinant polypeptide using a human host cell would not be within the scope of Claim 1 of the '755 patent?

A. That's correct.

Q. Because of the language that recites

"expressed in a nonhuman host"?

A. That's correct.

Q. Sorry, "produced in a nonhuman host."

A. "Produced in a nonhuman host."

Q. So that that language is limiting the process by which the recombinant polypeptide is prepared in a manner that it wouldn't be limited if the language were absent?

A. That's correct.

Q. You -- you used the term in your answer a moment ago and you also used it in your expert report -- you used the term "adjectival phrase."

A. Yes.

Q. I think you suggest in your expert report that "produced by a nonhuman host" is an adjectival phrase?

A. Right.

Q. It's your testimony that "produced" is being used as an adjective in the claim?

A. My testimony is that that phrase is being used as an adjective and that phrase has words in it which are nouns and verbs and

articles and so on, which, taken together in the grammatical structure of that sentence, have a meaning that is an adjective that modifies "a recombinant polypeptide." It says what kind.

Q. You said that that phrase has words in it which are verbs. Which words in that phrase are verbs?

A. Well, let me -- if I may --

(Witness peruses the exhibit.)

A. So we're talking -- the term now, just to be clear, is "produced by a nonhuman host transformed by a recombinant DNA molecule."

Q. That's the phrase that I'm talking about.

A. So the two verbs in there are "produced" and "transformed."

Q. You said in your expert report that that phrase describes the recombinant polypeptide. Do you recall saying that, or do you believe that to be the case?

A. Well, what it does, as you said a moment ago in one of your questions, is it puts limits or boundaries around what the recombinant polypeptide must be. It has to be produced. It

has to be one that's produced in a nonhuman host, for instance.

Q. That's a boundary on the process used to prepare the recombinant polypeptide; right?

A. Right.

Q. Are there other boundaries that this phrase that we've been talking about, "produced by a nonhuman host transformed by a recombinant DNA molecule" places on the recombinant polypeptide other than the process used to prepare the recombinant polypeptide?

A. I'm sorry, I'm trying to think through --

Q. Take as long as --

A. -- the implications of the word "boundaries."

Q. Take as long as you need to answer my question.

A. Okay.

(Pause from the record.)

A. No, I think it's as I said in my responsive report for Dr. Ravetch, that saying that a polypeptide is produced in a nonhuman host

transformed by a recombinant DNA molecule is just the longer and more precise way of saying recombinant DNA -- recombinant polypeptide except for the limitation that it has to come from a nonhuman cell line. So I think that's the boundary.

Q. Let me make sure I understand that because I think that's an answer to a different question than the one I was asking.

Are there any limitations on the recombinant polypeptide that are imposed by the language "produced by a nonhuman host transformed by a recombinant DNA molecule" other than limitations on how that recombinant DNA -- on how that recombinant polypeptide is prepared?

A. Okay. I missed an important part of your question, which was limitations on the recombinant DNA molecule. And no, I don't think there are.

Q. So that language, "produced by a nonhuman host transformed by a recombinant DNA molecule," only limits the process by which the recombinant polypeptide is prepared; correct?

A. I think that's right.

DAVID JACKSON

Q. It doesn't impose, in other words, any structural limitation on the recombinant polypeptide?

A. Well, in the context of the claim, I think it does impose a critical structural limitation in the sense that recombinant DNA molecules got to involve DNA. The DNA that has to be involved in this case is specified. And the specification of that DNA, in fact, as I've explained, does, in fact, specify the structure of the polypeptide.

Q. The DNA is specified not by the language we've been talking about, "produced by a nonhuman host transformed by a recombinant DNA molecule," but rather by the portion of the claim that begins with "A" in parentheses; right?

A. But the reference -- the "recombinant DNA molecule" reference within the language that we've been talking about does refer specifically to the specific DNA molecule as outlined in the part of the claim beginning "A."

Q. Right.

A. So in that sense, there's that connection between the languages we've been

talking about and lower parts of the claim.

Q. Right, but if you changed, for example, the set of DNA sequences within the scope of what we've been calling Limitation A, which are the DNA sequences that --

A. Right.

Q. -- hybridized to the probes; right?

A. Yes.

Q. Let's say you added five new probes and thereby added DNA sequences. That would change the scope of DNA sequences that could be in the recombinant DNA molecule; correct?

A. Uh-huh. So it would change the -- it would change the recombinant polypeptides that could be produced by nonhuman hosts transformed by those recombinant DNA molecules.

Q. Because you've changed the scope of what we've been calling A. And by "A," I mean where it says parentheses "A" and then it says, "The hybridizing to the probes."

A. Yes.

Q. And other than that section which defines the scope of the DNA sequences, is there anything else in the claim that limits the

primary structure of the recombinant polypeptide?

A. No, I don't think so.

Q. And is there anything -- again, limiting yourself to the claim language at issue here, "produced by a nonhuman host transformed by a recombinant DNA molecule" -- that imposes any limitation on the structure of the recombinant polypeptide?

MR. GROOMBRIDGE: Objection.

A. Other than the connection that I've been trying to explain between the reference to the recombinant DNA molecule in here and the specific sequences, no. But that seems to me to be a pretty important exception.

Q. If, for example, the language -- rather than "changes the scope of DNA sequences" in A, as we just did in the last hypothetical, we changed the language at issue, "produced by a nonhuman host transformed by a recombinant DNA molecule," let's say we just took it out completely for a moment --

A. Took out that entire phrase?

Q. Took out the entire phrase. It just says "Recombinant polypeptide" and then it

defined the scope of DNA sequences that correspond in A. Have I structurally changed the recombinant polypeptide? Have I removed any structural limitation on the recombinant polypeptide by doing that?

MR. GROOMBRIDGE: Objection.

A. Other than the one "introduced by the nonhuman host" portion of that phrase, I think not.

Q. Well, by removing that disputed language, I think we've agreed 30 minutes ago that I would -- I've thereby expanded the processes that can be used to prepare the recombinant polypeptide. I can now prepare it using a human host rather than a nonhuman host; right?

A. Right.

Q. Have I changed anything structurally? Have I broadened the structural definition of recombinant polypeptide by removing the language "produced by a nonhuman host transformed by a recombinant DNA molecule"?

A. Only in the broader sense of the term "polypeptide," which is one that has got

potential posttranslational modifications to it that will vary from one cell to another. So if you remove that nonhuman host restriction, there -- you might well have different structures that you would -- that would develop.

Q. Let me ask you the same question. I want you to apply the definition of polypeptide in the patent. Okay?

A. Apply --

Q. The patent's definition of polypeptide. Okay?

And my question is, if I remove the language "produced by a nonhuman host transformed by a recombinant DNA molecule," have I somehow enlarged the structural scope of recombinant polypeptide in Claim 1?

MR. GROOMBRIDGE: Objection.

A. Yeah, I think if you require that limiting definition of polypeptide, then that's -- that's correct.

Q. That I have not?

A. Yes.

Q. I've not enlarged the structural scope of recombinant polypeptide; is that what

you're saying?

A. Yes.

Q. If you apply the patent's definition of polypeptide?

A. Yes.

Q. Let me -- there's so many negatives, I just want to make the record clear. I think I know what you're saying.

But if one were to remove the language "produced by a nonhuman host transformed by a recombinant DNA molecule," it is correct that one would not enlarge the structural scope of the recombinant polypeptide of Claim 1 --

MR. GROOMBRIDGE: Objection.

Q. -- using the definition of polypeptide in the patent?

A. I believe that's correct.

Q. In your review of the '755 patent, did you find any novel clinical use for -- sorry -- for beta interferon that Dr. Fiers purports to have invented?

A. No.

Q. Did you find any novel treatment regimen?

A. No.

Q. Any novel composition with respect to adjuvants or carriers?

A. No.

Q. Any novel diseases that he claims can be treated by administration of beta interferon?

A. No.

Q. You'll agree that with respect to all of those parameters that I just asked you about, he teaches to administer beta interferon as it was administered in the prior art?

A. No, I wouldn't agree with that. I don't think he -- he teaches that the prior art has shown the potential for beta interferon. And he explicitly teaches that having much larger quantities of authentic beta interferon could expand the possibilities for treatment, both with respect to disease and with respect to regimen and dosage and so on.

Q. When you say "expand the possibilities," that is making the prior disclosed clinical uses and regimens more effective rather than having new regimens or new

diseases to be treated; right?

MR. GROOMBRIDGE: Objection.

A. No, not necessarily. I think it would certainly open up the possibility of finding new diseases to be treated.

Q. Does he disclose any of those anywhere?

A. He doesn't disclose any of those specifically, I don't believe.

Q. Generally --

A. Well, I think -- as I've said just now, what I think he does disclose is that the development of interferon as a therapeutic has been severely limited by its supply and that what he has done is to invent a method for overcoming that limitation with respect to supply in a way that's not just quantitative, but is so large as to be qualitative and to open up a whole variety of additional possibilities. I think that's a fair reading of the specification.

Q. And his method of overcoming that problem that he identifies in the art is a method for producing interferon beta; correct?

A. It's a method for -- that depends on

being able to produce a -- interferon beta in large quantities, and safely and all of this sort of thing, which can then be used in the step of administering a therapeutically effective amount of that to a patient needing treatment.

Q. And you've referred now a few times in your answers to other diseases that you can treat when you have more beta interferon. And I guess I still don't understand the basis for those answers. Is there something in the patent that identifies these new qualitative possibilities that are opened up with respect to treatment using beta interferon?

A. No. Fiers didn't specify any of those, and I'm not saying that he did. What I am saying is that the spectrum of viral diseases, for instance, which had been assessed using the limited quantities of beta interferon that were available was fairly limited.

That spectrum could have been and was expanded as interferons became much more widely available because they could be produced in larger quantities.

Same things with cancers. The

spectrum of tumor types that had been able to be investigated with the limited quantities was relatively limited and interferons -- recombinant interferons made possible to test a much broader variety with many different regimens in combination with other anticancer agents and so on. And he -- I mean, Fiers pretty clearly anticipates those possibilities.

Q. Does he demonstrate with any data whatsoever the utility of his beta interferon that he's prepared?

A. Well, he demonstrates by reference the utility of it. He -- the presumption is that if you make beta interferon and possibly even molecules which are just closely related to beta interferon by these recombinant techniques, then you can use those to treat diseases of various sorts.

And why do you think that? Well, because using the native material, it's already been done and there's already been some success indicated. That's a fair presumption.

Q. When you say he demonstrates the utility of it "by reference," you mean by

reference to prior art that disclosed the administration of beta interferon to treat various diseases?

A. Yes.

Q. Any disclosure of the pharmacokinetic properties of the recombinant beta interferon that you found in the '755 patent?

A. No.

Q. Any discussion or disclosure with respect to its toxicity?

A. I don't believe so.

Q. Any reference whatsoever to any of its pharmacological properties?

A. Well, again, by reference to the successful work that has been done, but not to specific detailed pharmacological properties.

Q. Any disclosure whatsoever of any pharmacological difference between the interferon beta that Dr. Fiers discloses how to produce and the native beta interferon?

A. No, but maybe I'm misunderstanding your question because I don't see how there could have been any such disclosure. I mean, he

certainly doesn't claim it, but if you haven't produced and tested the material, I don't -- I don't see how you're going to be able to disclose that.

Q. He couldn't have known about any such difference because he had never actually tested the beta interferon?

A. Right.

Q. By the way, you know Dr. Ravetch was deposed in this case; correct?

A. Yes.

Q. Did you read his transcript?

A. Yes -- oh, no, no, no. I have not seen -- I don't know anything about the content of his transcript.

Q. You didn't look at it?

A. No.

Q. So just to be clear -- sorry for that divergent [sic] -- the skilled artisan reading the '755 patent disclosure would not understand that Dr. Fiers was in possession of the idea of any pharmacological or other difference between the recombinant beta interferon and native beta interferon?

A. I think that's correct.

Q. You discussed the prosecution history somewhat with Mr. Barsky this morning, but I wanted to discuss some other aspects of it as well and make sure I understand what your position is.

(Jackson Exhibit 11, Bates Nos. BIMA0005496, Preliminary Amendment, marked for identification.)

BY MR. BERL:

Q. You've been handed what's been marked as Exhibit 11, which is entitled "Preliminary Amendment." It has a stamp on it of May 25, 1995. I'll represent to you that this is a preliminary amendment in the '930 application that --

A. '930.

Q. -- issued as the '755 patent.

If I could turn your attention to page 5, do you see where it says, "Add new Claims 31 through 34 as follows" in the middle?

A. Yes, right above the line.

Q. Right.

And then what follows are Claims 31,

32, 33 and 34; is that right?

A. Yes.

Q. And Claim 31 includes the language "produced by a host transformed by a recombinant DNA molecule"; is that right?

A. Yes.

Q. And Claim 32 does not include that language; right?

A. That's correct.

Q. And Claims 33 and 34, if you could turn to those on pages 6 and 7 --

A. Yes.

Q. -- they have before the amendment the method according to Claim 31 or 32.

Do you see that?

A. I do.

Q. And do you understand that to mean that the language of Claim 31 or 32 is included, by operation of law, in Claims 33 and 34?

A. I'm sorry, say that again.

Q. Do you understand that, by reference to or dependence on Claims 31 or 32, Claims 33 and 34 are incorporating the language from the referenced claims into their own claims?

A. Ah, yes.

Q. So when you said in your expert report that the "produced by" and "transformed" language that Dr. Ravetch pointed to does not appear anywhere in Claims 32 through 34, that's not exactly correct, is it?

MR. GROOMBRIDGE: Objection.

A. Well, it's certainly literally correct.

Q. But you understood, when you wrote that, that by operation of law, that language, "produced by a host transformed by a recombinant DNA molecule," was incorporated in the Claims 33 and 34; right?

A. Actually, when I wrote that, I don't think I did. I don't think it was until right now that I understood, when you made that point, that operation of law -- my understanding was that these were dependent claims.

Q. Right.

A. All right. And I actually believed, I thought, that the connection went in the opposite direction, if you'd like, that these two claims were associated with 31 and 32 and so it

would still be the case that, in 31, that was the only place that that language occurred.

Q. What do you mean, these two claims, 34 and 33, are associated with 31 and 32? What did you understand that to mean?

A. Well, I'm -- I had -- these had been identified as dependent claims.

Q. Okay.

A. And so that suggested to me that these were claims that then, in essence, illustrated the DNA sequence selected from the group, for instance --

Q. Did you think --

A. -- the illustration of it.

Q. Did you think you had sufficient expertise to be commenting and advising the court as to the meaning of these dependent claims?

A. Well, I thought I did. In this case I may not have.

Q. Did anyone look at your report after you wrote it?

A. I would assume they did.

Q. Did you -- I assume you and your lawyers engaged in the process of editing your

report?

A. Yes.

Q. Did you ask them about these dependent claims before you made a statement about what they did or did not include?

A. There was some discussion about the dependent claims, but it was mostly in terms of that they were identified as dependent claims.

Q. You see that all these claims in the '930 recite a method for treating human viruses?

A. Yes.

Q. Okay. Let's take a look at the '723 application that you reference as well in your expert report. And I've handed you what's been marked as Exhibit 12.

THE REPORTER: Not yet.

(Jackson Exhibit 12, Bates Nos. BIMA0010885 through 892, Preliminary Amendment, marked for identification.)

BY MR. BERL:

Q. You've now been handed what's been marked as Exhibit 12, which is a preliminary amendment in the '723 application.

A. Uh-huh.

DAVID JACKSON

Q. If you could look at page 5 of this preliminary amendment. Do you likewise see that it says, "Add new Claims 31 through 34"?

A. Yes.

Q. You see 31 has the language "produced by a host transformed by a recombinant DNA molecule"?

A. Right.

Q. 32 does not?

A. Right.

Q. And 33 and 34 depend from 31 or 32; right?

A. Yes.

Q. And these claims recite a method for amino modulation; is that right?

A. Yes.

Q. Could you go back to Exhibit 7, which was marked this morning. That was the --

A. What was that?

Q. -- rejection of the '930 application in September of 1996.

A. Here we go.

MR. GROOMBRIDGE: That's the one.

Q. Do you have it in hand?

A. I do.

Q. Do you understand that, in this rejection, on page 2, Claims 31 through 34 of the '930 application were rejected on grounds of double patenting over Claims 31 through 34 of the '723 application; right?

A. Yes.

Q. And in the middle of the page, the examiner says -- I'll just read it into the record and we'll discuss it in a moment -- "The positive process steps in Claims 31 through 34 of the instant application and Claims 31 through 34 respectively of the '723 application are identical. The only difference in the claims is in the preamble, i.e., the intended uses of the two processes. Since the actual process steps of the two sets of claims are the same, the scope of the two sets of claims is the same."

Do you see that?

A. Yes.

Q. You commented on that language in your expert report; is that right?

A. I believe so.

Q. The examiner is stating here that

the only difference between the claims of the '930 application and the '723 application is in the preamble; correct?

A. Yes.

Q. And that what's inside the preamble differs and what's outside the preamble is the same; is that right?

A. That's what the examiner is saying, yes.

Q. And outside the preamble is where the actual process steps are; correct?

A. So that gets into an issue of what constitutes the preamble. And --

Q. That's not what I'm asking you about. I'm asking you whether the examiner is saying here that what's outside the preamble is identical. You already said that's right.

A. Yes.

Q. And that what's outside the preamble is where you have the actual process steps.

A. So where does the examiner say that the actual process steps are outside the preamble?

Q. It says that the actual process

steps of the two sets of claims are the same; is that right?

A. Yes.

Q. And you just agreed with me, and I think it's clear from what the examiner said, that what's inside the preamble differs from the '903 and '723 and what's outside the preamble is the same.

A. Right.

Q. So what's outside the preamble is where the actual process steps are?

(Witness peruses the exhibit.)

A. What the examiner says is "The positive process steps in Claims 31 through 34 of the instant application and of the '723 are identical's. Okay.

So that could include the things that are outside the preamble, which the defendants are contending are the positive process steps.

But it could also include the language of administering -- the step of administering a composition to a patient in need of an effective amount, which is within the

preamble -- or what you're characterizing as the preamble.

And everything that the examiner says here would I think still be true because there are then still differences in what you're characterizing in the preamble, but there's nonetheless a positive process step, and, in fact, we believe the only positive process step, that is in the -- in the preamble.

Q. So --

A. So I think what the examiner says here is correct. But if I'm understanding you, I think you are not representing correctly or completely what the examiner was referring to here. I mean, as I've just explained it, I don't think there is any logical disconnect with what he says here and the fact that there's a positive step -- positive process step in the preamble that is identical in both of these patents.

Q. The examiner says the only difference in the claim is in the preamble; right?

A. He does.

Q. And then he says the actual process

steps of these claims are the same; correct?

A. That's right.

Q. Now --

A. So that could include the ones outside the preamble and the ones inside the preamble.

Q. It could include either, you think --

A. Okay.

Q. -- right?

A. I'm sorry?

Q. Yes, he could be referring to either of the steps inside the preamble or outside the preamble?

A. Yes, I'm agreeing with that.

Q. Either interpretation is reasonable?

A. (Nods head.)

Q. You need to answer audibly.

A. Well, I actually don't think that either interpretation is equally reasonable, as I've indicated before. I believe that what you're characterizing as positive process steps outside the preamble is, in fact, simply a phrase that modifies what kind of recombinant DNA

molecule is referred to in the positive process step.

Q. You said "positive process step," but he didn't say positive process step here; right? He said "positive process steps"?

A. Well, there are two patents and, therefore, there are two positive process steps that are the same in the preamble.

Q. Would you agree that he's drawing a distinction between the preamble and the rest of the claim?

A. Yes.

Q. You would agree that he's saying what's in the preamble is what's different?

A. Yes.

Q. You'd agree that what he's saying is outside the preamble is the same?

A. Yes.

Q. And he's saying that the actual process steps of the two sets of claims are the same?

A. Yes.

Q. And when you say the step of administering to, what does that step involve?

A. Well, it involves having a recombinant beta interferon that has been formulated in such a way that it's appropriate for administration to a human, presumably in the context of a clinical trial or a established approved treatment.

Q. So what do you actually do when you perform that step?

A. What do you actually do?

Q. Right.

A. You could do a variety of -- you could do a variety of things. As I think was outlined in the specification of the patent, even the limited clinical trials that had taken place up till that time had administered the interferon in a variety of different parenteral and oral routes as well. I think they referred to inhalation therapy and so on.

Q. So that administration step involves providing by some route of administration interferon to a patient; correct?

A. Yes.

Q. Certain amount of interferon; correct?

A. Yes.
Q. In a certain regimen?
A. Yes.
Q. For a certain amount of time?
A. Yes.
Q. That's the activity, so to speak, of the administration step?
A. Yes. You do all of those things when you're administering a recombinant polypeptide.
Q. Because you say administration is a step, you actually say it's the only step, and a step refers to some kind of action?
A. That's right.
Q. The action is what we just agreed upon, giving by some route of administration beta interferon to a patient in a certain amount for a certain amount of time; right?
A. Right.
Q. Now, why don't you go to the patent in Column 2. We looked at this before. Are you there?
A. Yes, I am.
Q. We looked at the bottom of Column 2

somewhat before. We talked -- we saw it's administered one to three times daily in dosages of 104 to 107 units.

Do you see that?

A. Yes.

Q. Then it says "the extent of the therapy depends on the patient and the condition being treated."

Do you see that?

A. Yes.

Q. Then it says, "Virus infections are usually treated by daily or twice daily doses over several days to two weeks."

Do you see that?

A. Yes.

Q. Then it says, "And tumors and cancers are usually treated by daily or multiple daily doses over several months or years."

Do you see that?

A. Yes.

Q. So the physical step of administering beta interferon to treat cancer is different from the physical step of administering beta interferon to treat a viral condition?

DAVID JACKSON

MR. GROOMBRIDGE: Objection.

A. No, I would not necessarily agree with that.

Q. Okay.

A. The length of time may be different.

Q. Do you recall two minutes ago when we agreed on what the physical step of administering beta interferon was?

MR. GROOMBRIDGE: Objection. Argumentative.

A. I think so.

Q. And you agreed with me that it's administering beta interferon by some route of administration in a certain amount for a certain length of time; correct?

A. Yes.

Q. And that administration is different for cancer versus viral conditions?

MR. GROOMBRIDGE: Objection.

A. No, I absolutely disagree with you, Mr. Berl --

Q. The length --

MR. GROOMBRIDGE: Just a second. Please let --

DAVID JACKSON

BY MR. BERL:

Q. Were you finished with your answer?

MR. GROOMBRIDGE: He obviously wasn't finished with his answer. Please restrain yourself and let him finish before you start talking.

MR. BERL: He paused. I thought he was finished.

MR. GROOMBRIDGE: It would do credit to the whole proceeding if we were all a little calmer.

MR. BERL: Thank you for your advice, yourself included.

BY MR. BERL:

Q. You can answer.

A. I disagree with that. In the first place, as I have said earlier, but maybe let me try to say it a little more precisely now, to characterize viral diseases as some single entity that can be treated by a single administration step, single defined administration step just is not correct. It is not how you treat diseases in the real world.

You have to figure out how those --

the viral disease responds best, if at all, to the treatment that you're applying and you can have quite different routes of treatment and different regimens of treatment.

That is even more true in the case of cancer, where there are tremendous variations between one sort of cancer and another that may well require different administration steps.

And so to say, as I understood you to be saying, that there are different ways of treating cancer and viral diseases with recombinant beta interferon is not correct.

That's not to say they're the same. It's that you can't make the categorization that all of viral diseases go one way, all the cancers go the other way.

Q. Are you finished with your answer yet?

A. I believe so.

Q. Now --

A. For the time being.

Q. Well, you can amend your remarks later.

Let's look at the patent. Okay.

A. Okay.

Q. Would you agree with me that the patent provides two lengths of treatment and categorizes them, one for viral conditions to be treated, then it says over several days to two weeks, and another one for tumors and cancers over several months or years?

A. What the patent says is that virus infections are usually treated by daily or twice daily doses over several days to two weeks, and tumors and cancers are usually treated by daily or multiple daily doses over several months or years.

So that certainly indicates that there are some circumstances in which those generalities don't apply. And again, I would say the amount of clinical research that had been done at this point in time --

Q. Were you done?

A. Back with us?

Q. I'm listening.

A. The amount of clinical research that had been done at this point in time was really quite limited. And so to be able to make any

generalizations, even these qualified generalizations, at this point was to some extent projecting things that weren't known.

Q. Let me ask you this: You understand that the specification is read through the lens of a person of ordinary skill?

A. Yes.

Q. You said that you believe you had the qualifications in 1980 of a person of ordinary skill?

A. Yes.

Q. Would a person of ordinary skill in the art read Column 2 to convey that the length of time for which one administers beta interferon is the same when one treats viral diseases as it is for treatment of cancer?

MR. GROOMBRIDGE: Objection.

A. Person of ordinary skill, and I'll use myself as an example, in 1980 would read this and say, hum, that's interesting. Maybe that's true, maybe that's not true. There's not enough data available at this point to really say.

Q. Okay. So let's take the patent at its word for a moment. Because I understand that

you say you wouldn't know for sure. But you would agree that the patent is disclosing two different time durations, one for antiviral diseases and another for cancer treatments?

A. What Fiers is doing is saying that in the research that's been done, it is usually, whatever that means, the case that the treatment for viral diseases has been shorter than the treatment for cancers has usually been. That's what he's saying.

Q. So that if one were practicing this claim based on the disclosure of the specification and one sought to administer beta interferon to treat a viral disease, one would follow the specification by administering the doses daily or twice daily over several days to two weeks; right?

MR. GROOMBRIDGE: Objection.

Q. I just read from the patent.

A. I know you read from the patent, but you read from the specification. Nobody is going to look at this paragraph -- no physician is going to look at this paragraph and say, Oh, jeez, I can't give beta interferon for a viral

disease for more than two weeks because this specification says usually that's what's done in a viral disease.

Nor are they going to say, Oh, jeez, if I'm going to treat this tumor, I've got to give beta interferon on a daily basis for a year because that's what it says in this specification. They're going to do clinical research that's going to determine that.

Fiers is making a -- a very general statement about a limited amount of research that had been done at that period of time.

Q. The general statement that he makes is that there's one time period or duration that's associated with treating viral conditions and a different duration that's associated with treating cancer; right?

A. In the research that had been done up until that time in the usual case for both viruses and cancer, that is true. That's what he said.

Q. So the administration step for treating cancer using the recombinant beta interferon polypeptide is different from the

administration step for treating a viral condition using the beta interferon polypeptide?

MR. GROOMBRIDGE: Objection.

A. In some circumstances, yes.

Q. And so when the examiner writes in what's been marked as Exhibit 7 that the actual process steps of the various claims are the same, the administration step would be understood to differ as between, for example, the '658 application that is directed to cancer and the '930 which is directed to treatment of viral diseases?

MR. GROOMBRIDGE: Objection.

A. No, the administration step is administration of a -- let's look at the claim and make sure I say it correctly.

(Witness peruses the exhibit.)

Q. Was your answer earlier about what the administration step is correct, or did you testify incorrectly about that?

A. Let's come back to that, can we, after I read this, after I made this point?

Q. You don't know whether your testimony was correct?

DAVID JACKSON

MR. GROOMBRIDGE: Just a second.

MR. BERL: I'm asking him a different question. I withdrew the last one.

BY MR. BERL:

Q. Was your testimony about what the administration constitutes earlier, about 15 minutes ago, correct, or would you somehow like to retract that?

A. Could you read back exactly what I said?

MR. GROOMBRIDGE: I believe --

Q. Do you believe you've said anything incorrect with respect to the meaning of the administration step?

A. How can I answer that question when I can't remember literally what I said? And you have the ability to read it back to me, so I can give you an accurate answer to that question.

Q. If you testified that the administration step was administering a certain amount of beta interferon by some route of administration for a certain period of time, would that testimony have been wrong?

DAVID JACKSON

A. I'm sorry, try that again.

Q. Sure.

If you testified earlier that the step of administering in these claims that we've been discussing refers to the administration by some route of a certain amount of beta interferon for a certain amount of time, would that testimony be wrong?

MR. GROOMBRIDGE: Objection.

A. I'm really sorry, but I'm having some kind of problem with the phraseology of that question. Can you ask it in another way?

Q. What are you having trouble understanding?

A. Well, if I knew that, I'd be able to tell you and to answer the question.

Q. Is it correct testimony that the step of administering refers to the administration by some route of a certain amount of beta interferon for a certain amount of time?

A. Yes.

Q. Okay.

A. Okay. And that will vary depending upon what is a therapeutic amount -- an effective

therapeutic amount --

Q. And that varies per the --

A. -- and what the disease is.

Q. That varies by the disease per the specification that we've been talking about for the last 15 minutes?

A. No, it varies by the disease in the real world as it is defined in the future relative to when this patent was -- was filed.

Q. But you understand that this term -- this claim has a fixed meaning as of the time of 1980?

A. I understand the claim's got a fixed meaning. What you keep talking about is the specification and talking as though the terminology in the specification is determinative with respect to this. And I don't think that's correct.

Q. But with respect to what a skilled artisan in 1980 would you have understood the administration step to mean with regard to different diseases, that would depend on the skilled artisan's understanding of the specification because all these future clinical

trials that you're talking about didn't exist in 1980; right?

MR. GROOMBRIDGE: Objection.

A. The skilled artisan in 1980 would have approached this specification, and particularly someone who knew what the current state of the art in clinical research using interferons was at that point, with a good deal of skepticism and said, Okay, that's Fiers' projection.

But you would have gotten approximately as many different opinions about this broad area of how to treat viral and cancer -- viral diseases and cancer with various interferons as there were people that you asked at that time.

Q. You don't hold the opinion, for example, that the duration of therapy for interferon to treat cancer is the same as it is to treat viral conditions, do you?

A. What I hold is that that duration for both cancers and viral diseases will vary from cancer to cancer and from viral disease to viral disease and there may well be circumstances

in which, for certain viral diseases, the effective treatment will take a longer period of treatment, for instance, than it does for certain cancers, for instance.

Q. Again, you've never treated a patient with cancer; right?

A. That's correct.

Q. You don't have an MD?

A. That's correct.

Q. You'll agree that if the step of administering beta interferon to treat cancer is different from the step of administering beta interferon to treat a viral condition, then the examiner cannot be referring to the administration step in Exhibit 7 when he says that the actual steps of the two sets of claims are the same; right?

MR. GROOMBRIDGE: Objection.

A. No, no, no. What the claim says is "The step of administering to a patient in need of such treatment a therapeutically effective amount of a composition comprising" -- hang on. I'm not finished with my answer yet.

Q. I'm asking you about the claims of

the application. You're reading from the patent. I'm asking about something different. I think you're confused?

A. Okay, I'm confused, then. What are the claims that you're asking about?

Q. Turn to Exhibit 7. And let me also mark for you, just so it's complete --

MR. BERL: Do you have Tab 10?

Q. -- Exhibit 13, which I'll show you in a second.

(Jackson Exhibit 13, Bates Nos. BIMA0010234 through 250, Amendment and Response, marked for identification.)

A. I don't think I have the actual claims --

Q. I've handed you what's been marked as Exhibit 13, which is an amendment in response to the '658 application.

What were you saying, Doctor?

A. Yes, in Exhibit 7, you said you wanted to look at the claims in Exhibit 7. And I don't think Exhibit 7 has got any actual claims in it, does it?

Q. Let me go through this so my

question is clear.

Do you see you've just been handed Exhibit 13, which is an amendment in response to the '658 application?

Do you see that?

A. Yes.

Q. Do you see that Claim 31 on page 2 refers to a method for treating human cancers or tumors comprising a step of administering, and it goes on?

Do you see that?

A. I do.

Q. And you have before you the claims of the '930 application by preliminary amendment. I believe that was Exhibit 10 -- Exhibit 11. Excuse me. Here's Exhibit 11.

And do you see that it has on page 5 -- we looked at this method for treating human viruses?

A. Yes.

Q. And you understand that there was a double-patenting rejection in the '930 application both over the claims to the '723 application for treatment of immunomodulation and

the '658 application Exhibit 13 for the treatment of cancers or tumors?

A. Yes.

Q. And you understand that the basis for the examiner's double-patenting rejections of the claims of the '930 applications is that the actual process steps are the same in the application so the scope of the claims is the same and you can't get two patents for that?

A. Yes.

Q. Do you understand that?

And my question for you, after we've looked now at Column 2 of the patent and we've had the discussion we had -- and I'll direct your attention, for example, to Exhibit 7, which was the rejection in the '723, there's also a rejection in the -- over the '658 application, which I'm happy to show you -- that -- where the examiner states, as you see here, the actual process steps of the two sets of claims are the same.

Do you see that?

A. Yes.

Q. My question is that -- given that a

skilled artisan would understand Dr. Fiers to be conveying in Column 2 that the duration of treatment is different for treating cancer than it is for treating viral conditions, a skilled artisan would have understood the examiner's statement that the actual process steps of the claims are the same not to refer to the step of treating since that step differs; right?

MR. GROOMBRIDGE: Objection.

A. No, I don't agree with that.

Q. Explain why you don't agree with that.

A. Because what's being claimed is the step of administering a therapeutically effective amount. And that encompasses a very large amount -- a very large number of potential ways of administering the compound, including different times, different amounts, different regimens and so on.

And so to say that the steps are different because in the specification Fiers summarizes some limited experience with viral diseases and some limited experience with cancer being treated with beta interferon, I think it

does not follow that you -- your claim saying that the examiner can't be referring to -- I'm sorry, I've lost my train of thought on this now.

Q. You'll agree that a skilled artisan wouldn't read Column 2 to convey that the administration to treat viral conditions is the same with respect to duration as the administration of beta interferon to treat cancer?

MR. GROOMBRIDGE: Objection.

A. Well, let me try again.

The skilled artisan reading that at the time I think would say, Okay, that's interesting, but not dispositive, and that there are likely to be many different variations, some of which will fall within what Fiers' summary is and some of which will not.

And so to conclude -- I don't think that the skilled artisan would have said that based on the information that they knew in the field, that -- that the generalizations that Fiers made, which he himself qualified, represent two nonoverlapping categories of how you treat two different sets of diseases.

DAVID JACKSON

Q. I didn't use the word "overlapping." I said you agree that a skilled artisan wouldn't read Column 2 to convey that the administration step to treat viral conditions is the same as the administration step to treat tumors; right?

A. That's right. That's right.

Q. Whether they overlap or not, clearly the specification identifies two different categories of duration of treatment for treating viral conditions as compared to treating tumors?

MR. GROOMBRIDGE: Objection.

Q. Sorry, you said yes?

A. No, I didn't say yes.

Q. Have you said anything? I thought I heard you say something.

A. No. That was Mr. Groombridge objecting.

MR. GROOMBRIDGE: What I said was "objection."

MR. BERL: Sorry, I misheard you.

A. I -- I do not agree that there is a medically useful functional difference that has been defined based on the work that Fiers is referring to at that -- at that time in the

specification in Column 2, I think it was.

Q. So what you're basically saying is that the skilled artisan would read Column 2 and essentially ignore it because it's not medically supported?

MR. GROOMBRIDGE: Objection. Argumentative.

A. No, I am not saying that. I am saying that that would be a -- one of many different useful inputs to what the skilled artisan at that time would use to formulate his or her own opinion. But that, as I said a minute ago, not a dispositive one by any means.

Q. It's the only one identified in the patent, though; right?

A. Yes, but the patent doesn't represent the totality of the real world.

Q. Okay. I understand that.

I'm asking you what a skilled artisan would understand from the patent. And I think we're on the same page.

THE WITNESS: Can I have your napkin for a minute?

MR. GROOMBRIDGE: By all means.

DAVID JACKSON

(Pause from the record.)

BY MR. BERL:

Q. Could you turn to Exhibit 8? We marked that this morning. It's labeled "Amendment and Response" in the '930 application, and it's dated March of 1997.

A. Exhibit 8.

Q. You have that?

A. March 24, 1997, yes. The '930.

Q. And you understand this was Biogen's response to the double-patenting rejection we looked at earlier over the claims of the '723 application?

A. Yes.

Q. And on the first page, Biogen writes, "Please cancel Claim 32."

Do you see that?

A. Yes.

Q. And then Claim 31 --

A. Right.

Q. -- is amended.

Do you see that?

A. Yes.

Q. And there are remarks starting on

page 3 that go over to Claim 4 [sic]?

Do you see that?

A. Yes.

Q. And if I could direct your attention to the first paragraph of page 4, in the second sentence.

Do you see that?

A. Sentence starting "The preamble"?

Q. Yes.

And it says -- well, do you see, first of all, that the amendment on page 2 added the medical conditions that previously were recited in the '723 and '658 applications of immunomodulation and cancer?

A. Yes.

Q. So it collapsed all of the clinical uses that used to be in three separate applications into one claim; correct?

A. Right.

Q. And on page 4, Biogen wrote, "The preamble of amended Claim 31 now recites the several intended uses incorporated from the claim preambles of the '723 and '658 applications for the positive process steps claimed."

Do you see that?

A. Yes.

Q. So he's referring -- Biogen and Fiers are referring here to Claim 31 as amended; correct?

A. That's right.

Q. And it says that recites the several intended uses for the positive process steps claimed; right?

A. Yes.

Q. And looking at Claim 31 on page 2, can you identify for me the positive process steps claimed?

A. The positive process step in there is the step of administering to a patient in need of such treatment a therapeutically effective amount of a composition. And I believe that the reference -- the use of the plural again refers to the fact that there were -- that same step was present in both the '723 and the -- I thought it was '930, but maybe it's '658 applications.

Q. This sentence is now referring to amended Claim 31 and what it recites; right?

MR. GROOMBRIDGE: Objection.

DAVID JACKSON

Argumentative.

Q. Well, it wasn't argumentative a minute ago when you agreed with me.

Do you still agree with me that this sentence is referring to what amended Claim 31 recites?

MR. GROOMBRIDGE: Just so the transcript is clear, my objection is to your tone of voice.

MR. BERL: Okay. That's somewhere in the Federal Rules.

BY MR. BERL:

Q. You can answer.

A. Preamble.

(Witness peruses the exhibit.)

A. I mean, I really do think this could be interpreted -- the positive process steps claimed "incorporated from the claim preambles of the '723 and '658 applications" could refer to the step that we've been disputing about all afternoon, the step of administering a therapeutically effective amount.

Q. And it's, in your view, referring to the same step that appears in multiple claims and

that's why it says "steps" there?

A. I think that's the most likely interpretation of that or that it was a -- a mistake. This language has been copied so many times in so many different exchanges with the examiner that I think there's probably some errors in this.

Q. Or it may be there weren't errors and it's just right and what Dr. Ravetch says it means is correct?

A. That's a possibility as well.

Q. Now, afterwards it says, "Applicant agrees to abandon the '723 and '658 applications if amended Claim 31 is allowed."

Do you see that?

A. Yes.

Q. So Biogen is not distinguishing its method of treatment claims that previously were present in the '658, '723 and '930 applications from each other; right?

A. In the sense -- you're saying they're not distinguishing them because they're putting them all in a single claim in a single patent?

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Q. Right.

A. Yes.

Q. They're not arguing that they're separably patentable and they should overcome the rejection; right?

A. That's right.

Q. They're simply agreeing with the examiner that they're not separably patentable and they're merging them all into the same claim; correct?

A. Yes.

MR. GROOMBRIDGE: I shall need to take a break.

MR. BERL: Why don't we take a break.

THE VIDEOGRAPHER: The time is approximately 4:13 p.m. This is the end of Media No. 4. We are off the record.

(Recess from the record.)

THE VIDEOGRAPHER: The time is approximately 4:30 p.m. This is the beginning of Media No. 5. We are on the record.

DAVID JACKSON

BY MR. BERL:

Q. Still feeling okay?

A. Yes.

Q. Nothing going wrong --

A. Right.

Q. -- medically?

Okay. You referred and we've referred several times today to prior art treatments using isolated interferon; correct?

A. Correct.

Q. Both alpha and beta.

In those cases, it was sometimes the case that the same hospital or entity would both isolate the interferon and then use it in a clinical trial to determine whether it could be useful to treat diseases; is that right?

A. I don't know that definitively.

Q. You don't know one way or the other?

A. Right.

MR. BERL: Let's take a look at the next exhibit, which is 14.

(Jackson Exhibit 14, No Bates numbers, Cancer Treatment Reports Volume 62, No. 11, November 1978, marked for

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identification.)

MR. BERL: For the record, Exhibit 14 is entitled, "Human Interferon and Its Inducers: Clinical program overview at Roswell Park Memorial Institute," by Carter, et al.

BY MR. BERL:

Q. Is there a reason that you're laughing about this?

A. Yes, but it's a private one.

Q. Is it anything pertinent in any way to the case?

A. I don't think so.

Q. Do you have some relationship with one of the authors?

A. I know Dr. Carter.

Q. Is there anything noteworthy about Dr. Carter as it relates to this article?

A. I don't know because I don't know this article.

Q. Why don't you take a moment to review it.

A. Sure.

(Witness peruses the exhibit.)

A. Okay.

Q. Have you had an opportunity to familiarize yourself with Exhibit 14?

A. Yes.

Q. It's an article published in November of 1978 by Carter in Cancer Treatment Reports?

A. Yes.

Q. And this is describing a program at the Roswell Park Memorial Institute in New York?

A. Yes.

Q. And this program it recites -- and I'm looking at the first column of the first page -- includes large-scale production and purification of hFIF; correct?

A. Right.

Q. That's interferon beta?

A. Yes.

Q. And, including other things, researching the clinical application of hFIF --

A. Right.

Q. -- correct, of interferon beta?

A. That's correct.

Q. So that this institute is both

generating interferon beta and administering interferon beta --

A. Right.

Q. -- to treat diseases; correct?

A. That's right.

Q. And this was part of the prior art relating to the treatment of disease using beta interferon; correct?

A. Yes.

Q. Now, you have discussed on several occasions today some of the challenges associated with expression of proteins recombinantly, especially including in host cells; right?

A. No, in bacterial host cells.

Q. I think you testified that there was even less available information regarding the expression of proteins in mammalian host cells as of 19- --

A. In 1980, that was certainly true.

Q. Now, all of the expression that we've talked about today has been expression of wild-type proteins; correct?

MR. GROOMBRIDGE: Objection.

A. By "wild-type," you mean proteins

coded by the sequence that was ultimately derived from messenger RNA coding for beta -- human beta interferon with --

Q. Sure.

A. -- presumably no mutation in it?

Q. Let's use that definition.

A. Okay. Yes.

Q. That's what you've been discussing today; correct?

A. Yes.

Q. That interferon -- that wild-type interferon, as you've defined it, would have the same amino acid sequence as the native beta interferon?

A. With the -- with the caveat that, as we've discussed earlier, beta interferon can be produced as a pre protein. And so if the processing were not appropriate in the host strain that was used, then the sequence might be different.

Q. Other than the cleavage of the pre sequence, the sequence is the same?

A. It should be.

Q. What was the state of the technology

with respect to making mutations so that the amino acid sequence of the recombinantly produced protein would differ from the native sequence and then treating diseases using that mutated sequence?

A. Well, can we break that question into two parts, what was the state of the technology with respect to making the changes and then come back to the treatment?

Q. Sure.

A. Okay. So the technology with respect to making the changes was it existed, it was still developing, it was not remotely as facile as it is today, as I discussed this morning; but the technique called oligonucleotide-directed mutagenesis where one synthesized a relatively small segment of DNA that incorporated a mutation that one wished to introduce and then introduced this DNA -- the segment of mutated DNA along with the wild-type DNA, transformed cells, you would get at a low frequency out of that -- you could expect to get the mutations that you were looking for.

So it existed. It was not perfect.

There were some -- as almost always the case, some situations where you thought it should work and it wouldn't, but it was -- it was an available technology that was an important one.

Q. That was -- what you just described was a directed mutagenesis approach where one identifies a particular mutation one wishes to make; correct?

A. That's right.

Q. Now, was there technology available for making numerous mutants?

A. Oh, sure.

Q. And producing all of them recombinantly?

A. Well, so that technologies that I'm thinking of for making numerous mutations was basically of, generally speaking, two sorts. One was to use ionizing radiation, either X-rays or ultraviolet light. And that would introduce, in the case of ionizing radiation, essentially random changes into DNA. In the case of ultraviolet light, they were mechanistically not random, but the genetic effect was roughly the same as if they had been -- if you were talking

about a large DNA molecule.

And then the second general class of approach in introducing these random mutations was to use chemical mutagens, things like ethylmethane sulphonate and various other DNA-reactive and modifying agents.

All of those approaches basically put mutations at random positions in the DNA that you were treating. And so you had to sort through a large number of mutants if what you were looking for was a particular one.

Q. And then with respect to expressing the mutants, it would be a process akin to a new project for expressing a new protein?

MR. GROOMBRIDGE: Objection.

A. Again, I don't think you can make an ironclad generalization about this. But with some specific kinds of exceptions that I can touch on if you would like, a number of the new random mutations that you would make would generate a protein that you might expect would be more likely than not to be able to be purified in much the same way without too many modifications as you purified the wild-type protein.

Now, the exceptions to that would be situations where either the mutation was one that introduced a premature termination codon into the decoding sequence, and so you wouldn't get a full-length protein.

And the other exception would be one -- and again, there's several specific examples of it; but, for instance, if you introduced a cysteine residue, and that could participate in inappropriate disulfide bond or, in many cases, it could cause in turn molecular reaction through the formation of disulfide bond, that might totally change the purification process that you would have to use.

Also, if you put certain hydrophobic residues in what turned out to be bad positions, that could change the folding pattern of your protein in such a way that it would have quite different physical characteristics.

Q. And you say in your report that making virtually any protein in functional form was a difficult, nonintuitive and unpredictable exercise. You discussed that part of your report earlier today.

A. Right.

Q. How would you compare that exercise with the process of, let's say, making a thousand different mutant forms of a given protein?

A. So can we be a little more explicit about what you mean by "making"? To make the mutations is trivial.

Q. Expressing them.

A. Making and expressing, which includes the purification and recovery of active protein, okay.

So using a thousand -- and the purpose of this exercise would be to find a particular mutation you're interested in amongst the thousand, or it would be to characterize all thousand --

Q. Characterize all thousand.

A. Okay. So to do the thousand proteins would be a lot of work, but each one would have a higher probability of your being able to at least do it successfully than for some random protein that was novel now and you're going to say, I want to express this and how do I do that?

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So it's the difference between a situation where, as I said before, for a particular protein that one might choose at random it was difficult, nonintuitive, a developing art, with a low probability of success, but you've only got one thing to work on. So you can focus a lot of effort and you can try to produce and purify -- express and purify that protein.

In the other case, your probability of technical success for each clone is going to be higher, but you've got a thousand things to work on rather than one.

They're both difficult projects.

Q. What if you had a million?

A. If you have a million, you've got to -- and realistically speaking, even if you had a thousand you've got to develop tricks that enable you to focus in on what you're interested in in this vast array of clones that you've got.

Q. And referring now more specifically to beta interferon, was there a known relationship between mutations one can make in the amino acid sequence and the functional

properties of the resulting protein?

A. There is now. Whether that was true in 1980, I don't know, but I doubt it.

Q. You're not aware of any kind of structure activity relationship that would identify which of the amino acids should be mutated in interferon beta to optimize its properties and to what amino acid they should be mutated?

A. I don't think there was any actual experimental data where people had made those such mutations and then asked the question, you know, what was the impact of it. There was certainly speculation that bore on the question of what kinds of mutations you might want to try to make first that started being made as soon as the sequence was available -- the DNA sequence was available.

Because, of course, you could then infer the amino acid sequence from that and you could draw certain conclusions from knowing that amino acid sequence.

Q. And when you say that speculation started being made --

A. Yes.

Q. -- are you referring to anything in particular, literature or . . .

A. I seem to remember reading that -- in one of Taniguchi's publications, I think he had commented on the fact that beta interferon is extremely hydrophobic and that that is likely to have certain consequences, in particular that it's likely to make it difficult to purify and more likely to aggregate with itself and with cell membranes and so on.

And if I remember correctly, in that same communication, he identified the fact that there were three cysteine residues in interferon and speculated that disulfide bond formation might be important and I think noted the fact that it was possible to form three different disulfide bonds, presumably only one of which was the correct one.

It wasn't known at that point, to the best of my knowledge, what the impact of forming an incorrect disulfide bond or indeed maybe even which disulfide bond was the correct one; but there was plenty of information from

other proteins that had been studied during the '60s and '70s to indicate that disulfide bonds were important, that they could perform incorrectly, and that the consequences for that were likely to be bad.

Q. Other than modification of the cysteine residues, which constitute three of the many residues in the sequence of interferon beta, would there have been any other basis to identify which amino acids should be mutated to optimize the properties of beta interferon?

A. I don't know of any at this point.

Q. And just so I understand your testimony, there was no technology available for kind of parallel expression of numerous mutant forms so that you can make a thousand at a time or something?

A. There were certainly technologies being developed at about that time. And again, I don't remember specifically when in the kind of 1980, '81 time frame, maybe even later than that, some of these came online.

One of the technologies that was under development -- and again, I can't remember

when it became broadly available -- was to do what's called an amino blot procedure where you can grow thousands to maybe 10,000 or so clones in 96-well plates, for instance, was I think the way it was first done.

You lyse the cells and then you use an antibody that's directed against beta interferon and you look to see which clones produce immunoreactive protein. That probably doesn't get you very far in terms of really whittling down this large number of clones, but it gets you usefully far. It's worth doing.

Subsequent technology, as I recall, was actually developed to the point that you could take a petri dish that just had a whole series of clones on it and essentially do the immunochemical reaction on the colonies that were lysed on the surface of the petri dish. And then the immunoreactivity of those colonies developed and you can get many more colonies on a petri dish than you can in a 96-well plate.

Q. Is there a particular time frame that you associate with the development of that technology or particular group of scientists?

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A. I can't remember who was doing it. I think a number of labs actually were working on that -- that sort of approach. And as far as the time frame goes, I just don't -- I don't remember that.

I think it was in the early '80s, but it may well have been later than the early 1980 time frame that we're talking about.

Q. You discussed introns in your expert report.

A. Yes.

Q. Are there any introns in the beta interferon gene?

A. Not in beta interferon, no.

MR. BERL: Why don't we take a couple-minute break and see if we have anything else.

MR. GROOMBRIDGE: Sounds great.

THE VIDEOGRAPHER: The time is approximately 4:53 p.m. We are off the record.

(Recess from the record.)

THE VIDEOGRAPHER: The time is approximately 5:02 p.m. We are back on the

record.

MR. BERL: We're ready. We have no more questions right now.

MR. GROOMBRIDGE: I just have a couple of follow-up questions.

EXAMINATION

BY MR. GROOMBRIDGE:

Q. Dr. Jackson, you mentioned at various times in your testimony the primary structure of a polypeptide.

What is that?

A. The primary structure is the -- generally agreed to be the sequence of amino acids running from the amino terminus to the carboxyl terminus. So it is just a list of the amino acid residues that comprises the polypeptide chain or the protein.

Q. Are there other kinds of structures apart from primary structures?

A. Yes.

Q. What other kinds are there?

A. Well, there is secondary structure, which is what are formed -- kinds of structures that are formed in relatively localized regions

of a protein when it starts to fold up into its ultimate active structure.

The two most common forms of secondary structure are the so-called alpha helix and the beta-pleated sheet. In fact, beta interferon has significant areas of beta-pleated sheet, which is one of the reasons it's such a sticky, and hydrophobic surfaces make it stick to membranes.

There is then what's called the tertiary structure. And that is the structure that's generally thought of as the active mature form of the single polypeptide chain. And that's where the polypeptide chain and the regions of secondary structure fold into what are generally an even more compact structure that, as I say, has the typical function that's associated with a protein.

And then finally, many proteins, in fact, act as parts of complexes. So there is what is known as quaternary structures, which is the structure that multiple polypeptide chains, which can be either identical or different from one another, assume to form a multichain

functional structure that is the operative structure in a cell.

Q. Does the polypeptide of the '755 patent have to fold in the right way in order to be biologically active?

MR. BERL: Objection.

A. Yes, it does.

Q. Now, one final thing.

Mr. Berl asked you about your mandate in this case, what it was that you were hired to do.

Do you remember that?

A. Yes.

Q. And as I recall, you said something to the effect that you had been hired as an expert to help in the claim construction phase of the case?

A. That's correct.

Q. Mr. Berl then mentioned something about the next phase of the case pertaining to patent validity.

Do you recall that?

A. I do.

Q. In the course of your analysis

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that's reflected in the two declarations we've seen in this, did you do anything in an effort to investigate issues pertaining to the validity or alleged invalidity of the '755 patent?

MR. BERL: Objection.

You can answer.

A. No, I did not.

MR. GROOMBRIDGE: Thank you.

Nothing further.

MR. BERL: If you can turn to your second -- Oh, do you want to go first? Go ahead.

MR. BARSKY: Okay. I just have a couple of quick questions.

EXAMINATION (Cont'd)

BY MR. BARSKY:

Q. You just testified -- you were just asked a question about the primary structure --

A. That's right.

Q. -- of a polypeptide.

Do you recall that?

A. I do.

Q. And then you were also asked about secondary, tertiary and quaternary structures as

well.

A. Correct.

Q. Those are all characteristics of proteins; correct?

A. Are you making a distinction between protein and polypeptide chain here?

Q. Yes.

A. Then the answer is no. They can be characteristics both of what you would call a protein, that is to say polypeptide chains that have some sort of covalent modification to it, and polypeptide chains, that is to say sequences of amino acids that have no -- no other covalent modifications to them.

There are plenty of proteins that -- there are plenty of polypeptide chains that don't have further covalent modifications that fold into secondary, tertiary and even quaternary structures.

Q. That are not proteins?

A. No, no, they are proteins. Proteins and polypeptide chains, I keep saying, are the same thing. They are used interchangeably. And in -- maybe a useful way to think of it is that

the category protein subsumes polypeptide chains as well as covalently modified polypeptide chains.

Q. Let me direct your attention back to what we discussed this morning about the use of the term "polypeptide."

Do you have that discussion in mind?

A. I do, indeed.

Q. In particular, I want to draw your attention back to the discussion and part of your report in which you distinguish between polypeptides or the general usage of the term "polypeptide" to the extent that it's different than a protein, "protein" to the extent it's different than a polypeptide.

Do you recall that?

A. I do recall that.

Q. Do you recall that in Column 8 of the '755 patent there's a specific definition of --

A. That's right.

Q. -- polypeptide?

A. Right.

Q. In each of the instances in which

you were talking about these different structures of what you called polypeptides, are you using that phrase, "polypeptide," in what you described this morning as the loose and interchangeable manner?

A. You mean during the course of the day?

Q. When Mr. Groombridge was just asking you questions.

A. Well, I thought I had just answered that question a minute ago. So let me try again.

There are polypeptides that in all respects would fit the definition that is in the '755 patent --

Q. Yes.

A. -- that have primary structure, have secondary structure, have tertiary structure and participate in quaternary structures.

Q. And my question to you was, are all of those polypeptides that fit into those categories also proteins?

A. Yes.

Q. Okay. Now, if we were to use the definitions -- the narrow definition of

polypeptide that appears --

A. Right.

Q. -- in the --

A. Right.

Q. -- '755 patent --

A. Right.

Q. -- using that definition, would you say that the polypeptides of -- as defined in Column 8 of the '755 patent --

A. Yes.

Q. -- and as distinct from proteins would also have those different structures --

MR. GROOMBRIDGE: Objection.

Q. -- in the secondary, tertiary and quaternary?

A. I really don't know how to say this more clearly than I have said it now about five times during the course of the day --

Q. You may have, but --

A. -- but let me try again.

So if you -- I don't understand the question that you're asking. Because it seems to me I've said very clearly that polypeptides, that is to say strings of amino acids without further

chemical modification -- covalent modification to them can participate in all four levels of structure.

What in addition to that do you need to know to answer your question?

And I've also said that all of those things can also be referred to as proteins and are proteins. They are both polypeptides and proteins, polypeptides by the '755 definition and proteins.

Q. Okay.

A. So now what else do you need to know?

Q. In those cases where you have what you've described as polypeptides within the meaning of the '755 patent --

A. Right.

Q. -- that have acquired these different secondary, tertiary and quaternary structures --

A. Right.

Q. -- in those cases, are the polypeptides themselves the same?

A. Well, except for the fact that

they're now folded into somewhat different three-dimensional structures, they're chemically the same.

Q. Okay.

A. They're chemically identical. You can denature them back to their random coil -- what you would call polypeptide chain form. And then you can renature them again and they will fold back up into the active structure.

Q. Okay. If you consider that the polypeptide is the linear chain that is described in the '755 patent in Column 8 or the linear array --

A. Yes.

Q. -- of a particular sequence, then would you say that those are identical regardless of these secondary, tertiary or quaternary structures? Referring just to the polypeptide that is defined in the '755 patent.

A. So do you think I have not said that? Do you think I've said something different from that? And if so, please tell me what, because I really don't understand what you're getting at.

DAVID JACKSON

Q. If you can answer my question.

A. So the answer is yes --

Q. Answer it again.

A. -- they are the same.

MR. BARSKY: Thank you.

That's all I have.

MR. BERL: I'm done, too.

MR. GROOMBRIDGE: Okay. I'm done as well. So we're all finished.

THE VIDEOGRAPHER: The time is approximately 5:13 p.m. This concludes Media No. 5 as well as today's deposition. We are off the record.